Glide 4.0

User Manual

Schrödinger Press

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Contents

Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Table 3.1.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, and screen output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the bar symbol `|` separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

Introduction

The *Glide User Manual* is intended to help you perform ligand database screening and high-accuracy docking with Glide™. Glide is run primarily from the Maestro™ graphical user interface, but can also be run from the command line. Online help is available in Maestro, although the information in this manual is generally more comprehensive.

Chapter 2 introduces the main features of Maestro and provides instructions for setting up your environment and running Maestro.

Chapter 3 introduces the scientific methods and computational procedures used in Glide.

Chapter 4 and Chapter 5 describe the preparation of the protein and the ligands for use in Glide.

Chapter 6 describes the use of the Receptor Grid Generation panel to calculate the grids that represent the receptor.

Chapter 7 describes the use of the Ligand Docking panel to set up and run docking jobs, and the use of atom-pair similarity, Glide constraints, and distributed processing of multiple-ligand docking calculations. It also describes the Glide Pose Viewer.

Chapter 8 contains information about running Glide, and its associated applications and utilities, from the command line.

1.1 Glide Panels

This section describes common features of the two main Glide panels. Controls that are specific to a panel appear in the middle section of the panel and are contained in a series of tabbed folders, or tabs.

1.1.1 Common Buttons

In the lower part of the two main panels, the following buttons appear:

Start

Click the Start button to open the Start dialog box. Section 1.1.2 summarizes starting Glide jobs using the Start dialog box.

Write

The Write button writes out all the files required for the job; however, the job will not actually be started. Once the run files (an input file, *jobname*`.inp`, and one or more input structure files, *jobname_structure*`.mae`) are written by Maestro, the Glide job can be run from the command line in a terminal window using the syntax:

`$SCHRODINGER/impact -i` *jobname*`.inp`

where *jobname*`.inp` is the Glide input file for the job in question. The log output is written to *jobname*`.log` by default; a different filename can be specified via `-o` *othername*`.log`.

Type `$SCHRODINGER/impact -h` for a usage summary of the `impact` command, or see Chapter 8 for a discussion of running Impact from the command line.

Reset

Resets the options in all the tabs to the default values.

Close

The Close button, which is located on all Maestro panels, dismisses the current panel without starting the job or writing any files.

Help

The Help button opens the Help panel with an appropriate help topic displayed.

1.1.2 Starting Jobs

Job options are set in the Start dialog box. The options depend on the type of Glide job which is being launched, and include the following:

Output Section

For Glide Receptor Grid Generation, the Output section contains a unique feature, the Directory for grid files text box and Browse button. See Chapter 6 for more information.

Job Section

- Name—Type the name of the job in this text box, or accept the default name. When the job is started, the job name is used as the base name for files associated with the job. The Start dialog box for Glide jobs supplies an appropriate default name for each type of job (for example, `glide_dock`). However, a new default name is not automatically supplied each time you run a job of the same type. To avoid overwriting the job files from a docking job named `glide_dock`, use new names for the second and subsequent docking jobs.

> **Note:** Glide does *not* automatically assign new names to jobs or files. If files of the same name exist, a warning is displayed before any files are overwritten.

- Host—Choose a host, if you want to run the job on a remote machine. This option menu displays all the hosts defined in the `$SCHRODINGER/schrodinger.hosts` file, with the number of processors on the host in parentheses. The default is `localhost`.
- Username—Enter your user name, if it is required for running the job on remote machines. The default value is the user name of the user who started Maestro. If this user name is not correct for the selected host, you can change it in this text box. If the job is running locally, this text box is ignored.
- CPUs—Specify the number of CPUs to use to run the job.

Once you have finished setting these options, you can click Start to start the job.

1.2 Documentation

For information related to the installation and use of Glide, see the following documentation:

- The *Installation Guide*, which includes installation instructions for all Schrödinger products and documentation.
- The *Glide Quick Start Guide*, which contains tutorials intended to familiarize you with protein preparation, receptor grid generation, ligand docking, and the Pose Viewer.
- The *Impact Command Reference Manual*, which contains syntax and keywords for Impact command input files.
- The *Maestro User Manual*, which describes how to use the features of Maestro, including the Atom Selection dialog box. An appendix describes command-line utilities, many of which are used in Glide.
- The *Maestro Command Reference Manual*, which contains commands, options, and arguments for running Maestro from the command line, including the Atom Specification Language (ASL) and the Entry Specification Language (ESL).

1.3 Citing Glide in Publications

The use of this product should be acknowledged in publications as:

Glide, version 4.0, Schrödinger, LLC, New York, NY, 2005.

Introduction to Maestro

Maestro is the graphical user interface for all of Schrödinger's products: CombiGlide™, Epik™, Glide™, Impact™, Jaguar™, Liaison™, LigPrep™, MacroModel®, Phase™, Prime™, QikProp™, QSite™, SiteMap™, and Strike™. It contains tools for building, displaying, and manipulating chemical structures; for organizing, loading, and storing these structures and associated data; and for setting up, monitoring, and visualizing the results of calculations on these structures. This chapter provides a brief introduction to Maestro and some of its capabilities. For more information on any of the topics in this chapter, see the *Maestro User Manual*.

2.1 General Interface Behavior

Most Maestro panels are amodal: more than one panel can be open at a time, and a panel need not be closed for an action to be carried out. Each Maestro panel has a Close button so you can hide the panel from view.

Maestro supports the mouse functions common to many graphical user interfaces. The left button is used for choosing menu items, clicking buttons, and selecting objects by clicking or dragging. This button is also used for resizing and moving panels. The right button displays a shortcut menu. Other common mouse functions are supported, such as using the mouse in combination with the SHIFT or CTRL keys to select a range of items and select or deselect a single item without affecting other items.

In addition, the mouse buttons are used for special functions described later in this chapter. These functions assume that you have a three-button mouse. If you have a two-button mouse, ensure that it is configured for three-button mouse simulation (the middle mouse button is simulated by pressing or holding down both buttons simultaneously).

2.2 Starting Maestro

Before starting Maestro, you must first set the `SCHRODINGER` environment variable to point to the installation directory. To set this variable, enter the following command at a shell prompt:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

You might also need to set the DISPLAY environment variable, if it is not set automatically when you log in. To determine if you need to set this variable, enter the command:

```
echo $DISPLAY
```

If the response is a blank line, set the variable by entering the following command:

csh/tcsh: `setenv DISPLAY` *display-machine-name*`:0.0`

bash/ksh: `export DISPLAY=`*display-machine-name*`:0.0`

After you set the SCHRODINGER and DISPLAY environment variables, you can start Maestro using the command:

`$SCHRODINGER/maestro` *options*

If you add the $SCHRODINGER directory to your path, you only need to enter the command maestro. Options for this command are given in Section 2.1 of the *Maestro User Manual*.

The directory from which you started Maestro is Maestro's current working directory, and all data files are written to and read from this directory unless otherwise specified (see Section 2.8 on page 27). You can change directories by entering the following command in the command input area (see page 8) of the main window:

`cd` *directory-name*

where *directory-name* is either a full path or a relative path.

2.3 The Maestro Main Window

The Maestro main window is shown in Figure 2.1 on page 7. The main window components are listed below.

The following components are always visible:

- **Title bar**—displays the Maestro version, the project name (if there is one) and the current working directory.
- **Auto-Help**—automatically displays context-sensitive help.
- **Menu bar**—provides access to panels.
- **Workspace**—displays molecular structures and other 3D graphical objects.

The following components can be displayed or hidden by choosing the component from the Display menu. Your choice of which main window components are displayed is persistent between Maestro sessions.

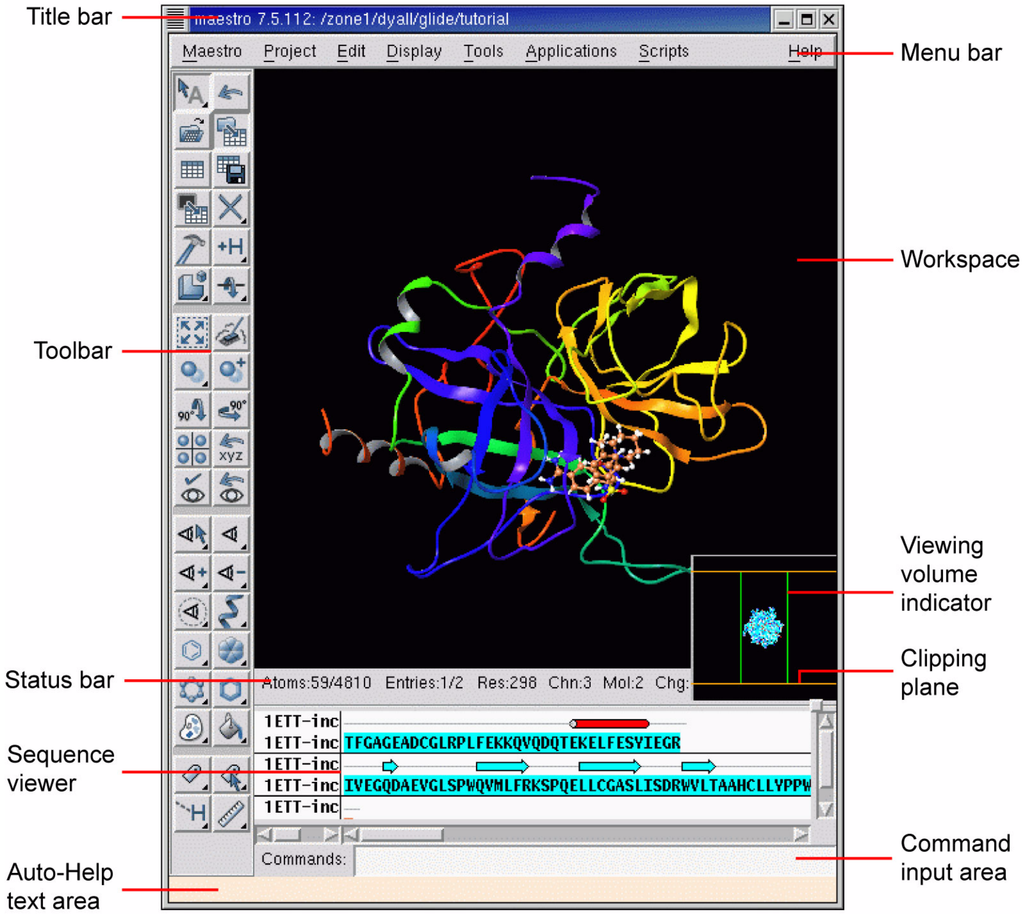


Figure 2.1. The Maestro main window.

- **Toolbar**—contains buttons for many common tasks and provides tools for displaying and manipulating structures, as well as organizing the Workspace.
- **Status bar**—displays information about a particular atom, or about structures in the Workspace, depending on where the pointer pauses (see Section 2.5 of the *Maestro User Manual* for details):
  - **Atom**—displays the chain, residue number, element, PDB atom name, formal charge, and title or entry name (this last field is set by choosing Preferences from the Maestro menu and selecting the Feedback folder).
  - **Workspace**—displays the number of atoms, entries, residues, chains, and molecules in the Workspace.

- **Clipping planes window**—displays a small, top view of the Workspace and shows the clipping planes and viewing volume indicators.
- **Sequence viewer**—shows the sequences for proteins displayed in the Workspace. See Section 2.6 of the *Maestro User Manual* for details.
- **Command input area**—provides a place to enter Maestro commands.

When a distinction between components in the main window and those in other panels is needed, the term *main* is applied to the main window components (e.g., main toolbar).

You can expand the Workspace to occupy the full screen, by pressing CTRL+=. All other components and panels are hidden. To return to the previous display, press CTRL+= again.

2.3.1 The Menu Bar

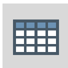
The menus on the main menu bar provide access to panels, allow you to execute commands, and control the appearance of the Workspace. The main menus are as follows:

- Maestro—save or print images in the Workspace, execute system commands, save or load a panel layout, set preferences, set up Maestro command aliases, and quit Maestro.
- Project—open and close projects, import and export structures, make a snapshot, and annotate a project. These actions can also be performed from the Project Table panel. For more information, see Section 2.4 on page 13.
- Edit—undo actions, build and modify structures, define command scripts and macros, and find atoms in the Workspace.
- Display—control the display of the contents of the Workspace, arrange panels, and display or hide main window components.
- Tools—group atoms; measure, align, and superimpose structures; and view and visualize data.
- Applications—set up, submit, and monitor jobs for Schrödinger's computational programs. Some products have a submenu from which you can choose the task to be performed.
- Scripts—manage and install Python scripts that come with the distribution and scripts that you create yourself. (See Chapter 13 of the *Maestro User Manual* for details.)
- Help—open the Help panel, the PDF documentation index, or information panels; run a demonstration; and display or hide Balloon Help (tooltips).

2.3.2 The Toolbar

The main toolbar contains three kinds of buttons for performing common tasks:

Action—Perform a simple task, like clearing the Workspace.



Display—Open or close a panel or open a dialog box, such as the Project Table panel.

Menu—Display a *button menu*. These buttons have a triangle in the lower right corner.

There are four types of items on button menus, and all four types can be on the same menu (see Figure 2.2):

- **Action**—Perform an action immediately.
- **Display**—Open a panel or dialog box.
- **Object types for selection**—Choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The object type is marked on the menu with a red diamond and the button is indented to indicate the action to be performed.
- **Other setting**—Set a state, choose an attribute, or choose a parameter and click on atoms in the Workspace to display or change that parameter.

The toolbar buttons are described below. Some descriptions refer to features not described in this chapter. See the *Maestro User Manual* for a fuller description of these features.

Figure 2.2. The Workspace selection ***button menu and the*** Adjust distances, angles or dihedrals ***button menu.***


Workspace selection
– Choose an object type for selecting
– Open the Atom Selection dialog box


Undo/Redo
Undo or redo the last action. Performs the same function as the Undo item on the Edit menu, and changes to an arrow pointing in the opposite direction when an Undo has been performed, indicating that its next action is Redo.

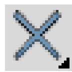

Open a project
Open the Open Project dialog box.


Import structures
Open the Import panel.


Open/Close Project Table
Open the Project Table panel or close it if it is open.


Save as
Open the Save Project As dialog box, to save the project with a new name.

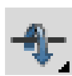

Create entry from Workspace
Open a dialog box in which you can create an entry in the current project using the contents of the Workspace.

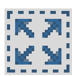

Delete
– Choose an object type for deletion
– Delete hydrogens and waters
– Open the Atom Selection dialog box
– Delete other items associated with the structures in the Workspace
– Click to select atoms to delete
– Double-click to delete all atoms


Open/Close Build panel
Open the Build panel or close it if it is open.


Add hydrogens
– Choose an object type for applying a hydrogen treatment
– Open the Atom Selection dialog box
– Click to select atoms to treat
– Double-click to apply to all atoms


Local transformation
– Choose an object type for transforming
– Click to select atoms to transform
– Open the Advanced Transformations panel


Adjust distances, angles or dihedrals
– Choose a parameter for adjusting
– Delete adjustments


Fit to screen
Scale the displayed structure to fit into the Workspace and reset the center of rotation.


Clear Workspace
Clear all atoms from the Workspace.

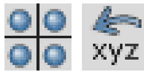

Set fog display state
Choose a fog state. Automatic means fog is on when there are more than 40 atoms in the Workspace, otherwise it is off.


Enhance depth cues
Optimize fogging and other depth cues based on what is in the Workspace.

Rotate around X axis by 90 degrees
Rotate the Workspace contents around the X axis by 90 degrees.

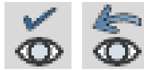
Rotate around Y axis by 90 degrees
Rotate the Workspace contents around the Y axis by 90 degrees.

Tile entries
Arrange entries in a rectangular grid in the Workspace.



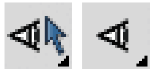
Reset Workspace
Reset the rotation, translation, and zoom of the Workspace to the default state.

Save view
Save the current view of the Workspace: orientation, location, and zoom.



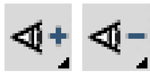
Restore view
Restore the last saved view of the Workspace: orientation, location, and zoom.

Display only selected atoms
– Choose an object type for displaying
– Click to select atoms to display
– Double-click to display all atoms



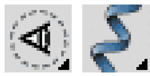
Display only
– Choose a predefined atom category
– Open the Atom Selection dialog box

Also display
– Choose a predefined atom category
– Open the Atom Selection dialog box



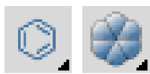
Undisplay
– Choose a predefined atom category
– Open the Atom Selection dialog box

Display residues within N angstroms of currently displayed atoms
– Choose a radius
– Open a dialog box to set a value



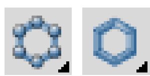
Show, hide, or color ribbons
– Choose to show or hide ribbons
– Choose a color scheme for coloring ribbons

Draw bonds in wire
– Choose an object type for drawing bonds in wire representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms



Draw atoms in CPK
– Choose an object type for drawing bonds in CPK representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in Ball & Stick
– Choose an object type for drawing bonds in Ball & Stick representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

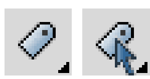


Draw bonds in tube
– Choose an object type for drawing bonds in tube representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Color all atoms by scheme
Choose a predefined color scheme.

Color residue by constant color
– Choose a color for applying to residues
– Click to select residues to color
– Double-click to color all atoms

Label atoms
– Choose a predefined label type
– Delete labels



Label picked atoms
– Choose an object type for labeling atoms
– Open the Atom Selection dialog box
– Open the Atom Labels panel at the Composition folder
– Delete labels
– Click to select atoms to label
– Double-click to label all atoms

Display H-bonds
– Choose bond type:
intra—displays H-bonds within the selected molecule
inter—displays H-bonds between the selected molecule and all other atoms.
– Delete H-bonds
– Click to select molecule

Measure distances, angles or dihedrals
– Choose a parameter for displaying measurements
– Delete measurements
– Click to select atoms for measurement

2.3.3 Mouse Functions in the Workspace

The left mouse button is used for selecting objects. You can either click on a single atom or bond, or you can drag to select multiple objects. The right mouse button opens shortcut menus, which are described in Section 2.7 of the *Maestro User Manual*.

The middle and right mouse buttons can be used on their own and in combination with the SHIFT and CTRL keys to perform common operations, such as rotating, translating, centering, adjusting, and zooming.

Table 2.1. Mapping of Workspace operations to mouse actions.

Mouse Button	Keyboard	Motion	Action
Left		click, drag	Select
Left	SHIFT	click, drag	Toggle the selection
Middle		drag	Rotate about X and Y axes Adjust bond, angle, or dihedral
Middle	SHIFT	drag vertically	Rotate about X axis
Middle	SHIFT	drag horizontally	Rotate about Y axis
Middle	CTRL	drag horizontally	Rotate about Z axis
Middle	SHIFT + CTRL	drag horizontally	Zoom
Right		click	Spot-center on selection
Right		click and hold	Display shortcut menu
Right		drag	Translate in the X-Y plane
Right	SHIFT	drag vertically	Translate along the X axis
Right	SHIFT	drag horizontally	Translate along the Y axis
Right	CTRL	drag horizontally	Translate along the Z axis
Middle & Right		drag horizontally	Zoom

2.3.4 Shortcut Key Combinations

Some frequently used operations have been assigned shortcut key combinations. The shortcuts available in the main window are described in Table 2.2.

Table 2.2. Shortcut keys in the Maestro main window.

Keys	Action	Equivalent Menu Choices
CTRL+B	Open Build panel	Edit > Build
CTRL+C	Create entry	Project > Create Entry From Workspace
CTRL+E	Open Command Script Editor panel	Edit > Command Script Editor
CTRL+F	Open Find Atoms panel	Edit > Find
CTRL+H	Open Help panel	Help > Help
CTRL+I	Open Import panel	Project > Import Structures
CTRL+M	Open Measurements panel	Tools > Measurements
CTRL+N	Create new project	Project > New
CTRL+O	Open project	Project > Open
CTRL+P	Print	Maestro > Print
CTRL+Q	Quit	Maestro > Quit
CTRL+S	Open Sets panel	Tools > Sets
CTRL+T	Open Project Table panel	Project > Show Table
CTRL+W	Close project	Project > Close
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo
CTRL+=	Enter and exit full screen mode (Workspace occupies full screen)	None

2.4 Maestro Projects

All the work you do in Maestro is done within a *project*. A project consists of a set of *entries*, each of which contains one or more chemical structures and their associated data. In any Maestro session, there can be only one Maestro project open. If you do not specify a project when you start Maestro, a *scratch* project is created. You can work in a scratch project without saving it, but you must save it in order to use it in future sessions. When you save or close a project, all the view transformations (rotation, translation, and zoom) are saved with it. When you close a project, a new scratch project is automatically created.

Likewise, if there is no entry displayed in the Workspace, Maestro creates a *scratch* entry. Structures that you build in the Workspace constitute a scratch entry until you save the structures as project entries. The scratch entry is not saved with the project unless you explicitly add it to the project. However, you can use a scratch entry as input for some calculations.

To add a scratch entry to a project, do one of the following:

- Click the Create entry from Workspace button:

- Choose Create Entry from Workspace from the Project menu.
- Press CTRL+C.

In the dialog box, enter a name and a title for the entry. The entry name is used internally to identify the entry and can be modified by Maestro. The title can be set or changed by the user, but is not otherwise modified by Maestro.

Once an entry has been incorporated into the project, its structures and their data are represented by a row in the Project Table. Each row contains the row number, an icon indicating whether the entry is displayed in the Workspace (the In column), the entry title, a button to open the Surfaces panel if the entry has surfaces, the entry name, and any entry properties. The row number is not a property of the entry.

Entries can be collected into groups, and the members of the group can be displayed or hidden. Most additions of multiple entries to the Project Table are done as entry groups.

You can use entries as input for all of the computational programs—Glide, Impact, Jaguar, Liaison, LigPrep, MacroModel, Phase, Prime, QikProp, QSite, and Strike. You can select entries as input for the ePlayer, which displays the selected structures in sequence. You can also duplicate, combine, rename, and sort entries; create properties; import structures as entries; and export structures and properties from entries in various formats.

To open the Project Table panel, do one of the following:

- Click the Open/Close Project Table button on the toolbar

- Choose Show Table from the Project menu
- Press CTRL+T.

The Project Table panel contains a menu bar, a toolbar, and the table itself.

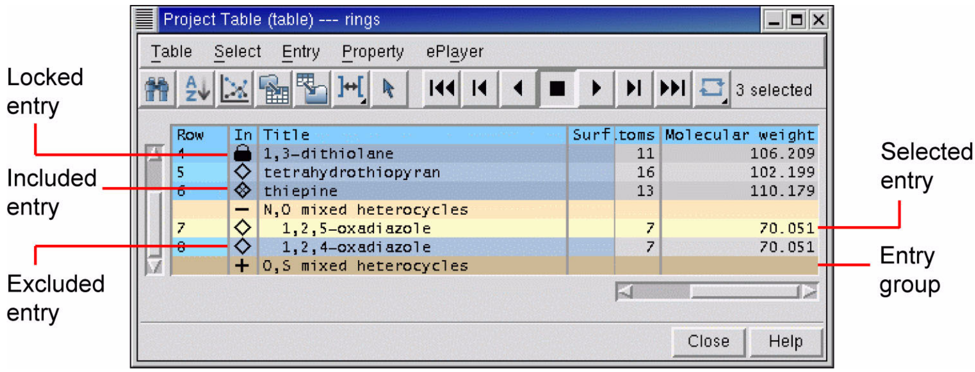
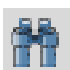


Figure 2.3. The Project Table ***panel.***

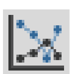
2.4.1 The Project Table Toolbar

The Project Table toolbar contains two groups of buttons and a status display. The first set of buttons opens various panels that allow you to perform functions on the entries in the Project Table. The second set of buttons controls the ePlayer, which "plays through" the selected structures: each structure is displayed in the Workspace in sequence, at a given time interval. See Section 2.3.2 on page 9 for a description of the types of toolbar buttons. The buttons are described below.



Find
Open the Find panel for locating alphanumeric text in any column of the Project Table, except for the row number.

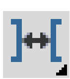
Sort
Open the Sort panel for sorting entries by up to three properties.



Plot
Open the Plot panel for plotting entry properties.

Import Structure
Open the Import panel for importing structures into the project.

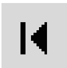
Export Structure
Open the Export panel for exporting structures to a file.



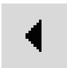
Columns
Choose an option for adjusting the column widths.

Select only
Open the Entry Selection dialog box for selecting entries based on criteria for entry properties.

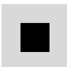
Go to start
Display the first selected structure.



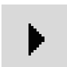
Previous
Display the previous structure in the list of selected structures.



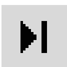
Play backward
Display the selected structures in sequence, moving toward the first.



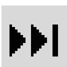
Stop
Stop the ePlayer.



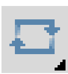
Play forward
Display the selected structures in sequence, moving toward the last.



Next
Display the next structure in the list of selected structures.



Go to end
Display the last selected structure.



Loop
Choose an option for repeating the display of the structures. Single Direction displays structures in a single direction, then repeats. Oscillate reverses direction each time the beginning or end of the list is reached.

The status display, to the right of the toolbar buttons, shows the number of selected entries. When you pause the cursor over the status display, the Balloon Help shows the total number of entries, the number shown in the table, the number selected, and the number included in the Workspace.

2.4.2 The Project Table Menus

- Table—find text, sort entries, plot properties, import and export structures, and configure the Project Table.
- Select—select all entries, none, invert your selection, or select classes of entries using the Entry Selection dialog box and the Filter panel.
- Entry—include or exclude entries from the Workspace, display or hide entries in the Project Table, and perform various operations on the selected entries.
- Property—display and manipulate entry properties in the Project Table.
- ePlayer—view entries in succession, stop, reverse, and set the ePlayer options.

2.4.3 Selecting Entries

Many operations in Maestro are performed on the entries selected in the Project Table. The Project Table functions much like any other table: select rows by clicking, shift-clicking, and control-clicking. However, because clicking in an editable cell of a selected row enters edit mode, you should click in the Row column to select entries. See Section 2.4.5 on page 18 for more information on mouse actions in the Project Table. There are shortcuts for selecting classes of entries on the Select menu.

In addition to selecting entries manually, you can select entries that meet a combination of conditions on their properties. Such combinations of conditions are called *filters*. Filters are Entry Selection Language (ESL) expressions and are evaluated at the time they are applied. For example, if you want to set up a Glide job that uses ligands with a low molecular weight (say, less than 300) and that has certain QikProp properties, you can set up a filter and use it to select entries for the job. If you save the filter, you can use it again on a different set of ligands that meet the same selection criteria.

To create a filter:

1. Do one of the following:
   - Choose Only, Add, or Deselect from the Select menu.
   - Click the Entry selection button on the toolbar.

2. In the Properties folder, select a property from the property list, then select a condition.
3. Combine this selection with the current filter by clicking Add, Subtract, or Intersect. These buttons perform the Boolean operations OR, AND NOT, and AND on the corresponding ESL expressions.
4. To save the filter for future use click Create Filter, enter a name, and click OK.
5. Click OK to apply the filter immediately.

2.4.4 Including Entries in the Workspace

In addition to selecting entries, you can also use the Project Table to control which entries are displayed in the Workspace. An entry that is displayed in the Workspace is *included* in the Workspace; likewise, an entry that is not displayed is *excluded*. Included entries are marked by an X in the diamond in the In column; excluded entries are marked by an empty diamond. Entry inclusion is completely independent of entry selection.

To include or exclude entries, click, shift-click, or control-click in the In column of the entries, or select entries and choose Include or Exclude from the Entry menu. Inclusion with the mouse works just like selection: when you include an entry by clicking, all other entries are excluded.

It is sometimes useful to keep one entry in the Workspace and include others one by one: for example, a receptor and a set of ligands. You can fix the receptor in the Workspace by selecting it in the Project Table and choosing Fix from the Entry menu or by pressing CTRL+F. A padlock icon replaces the diamond in the In column to denote a *fixed* entry. To remove a fixed entry from the Workspace, you must exclude it explicitly (CTRL+X). It is not affected by the inclusion or exclusion of other entries. Fixing an entry affects only its inclusion; you can still rotate, translate, or modify the structure.

2.4.5 Mouse Functions in the Project Table

The Project Table supports the standard use of shift-click and control-click to select objects. This behavior applies to the selection of entries and the inclusion of entries in the Workspace. You can also drag to resize rows and columns and to move rows.

You can drag a set of non-contiguous entries to reposition them in the Project Table. When you release the mouse button, the entries are placed after the first unselected entry that precedes the entry on which the cursor is resting. For example, if you select entries 2, 4, and 6, and release the mouse button on entry 3, these three entries are placed after entry 1, because entry 1 is the first unselected entry that precedes entry 3. To move entries to the top of the table, drag them above the top of the table; to move entries to the end of the table, drag them below the end of the table.

A summary of mouse functions in the Project Table is provided in Table 2.3.

Table 2.3. Mouse operations in the Project Table.

Task	Mouse Operation
Change a Boolean property value	Click repeatedly in a cell to cycle through the possible values (On, Off, Clear)
Display the Entry menu for an entry	Right-click anywhere in the entry. If the entry is not selected, it becomes the selected entry. If the entry is selected, the action is applied to all selected entries.
Display a version of the Property menu for a property	Right-click in the column header
Edit the text or the value in a table cell	Click in the cell and edit the text or value
Include an entry in the Workspace, exclude all others	Click the In column of the entry

Table 2.3. Mouse operations in the Project Table. (Continued)

Task	Mouse Operation
Move selected entries	Drag the entries
Paste text into a table cell	Middle-click
Resize rows or columns	Drag the boundary with the middle mouse button
Select an entry, deselect all others	For an unselected entry, click anywhere in the row except the In column; for a selected entry, click the row number.
Select or include multiple entries	Click the first entry then shift-click the last entry
Toggle the selection or inclusion state	Control-click the entry or the In column

2.4.6 Project Table Shortcut Keys

Some frequently used project operations have been assigned shortcut key combinations. The shortcuts, their functions, and their menu equivalents are listed in Table 2.4.

Table 2.4. Shortcut keys in the Project Table.

Keys	Action	Equivalent Menu Choices
CTRL+A	Select all entries	Select > All
CTRL+F	Fix entry in Workspace	Entry > Fix
CTRL+I	Open Import panel	Table > Import Structures
CTRL+N	Include only selected entries	Entry > Include Only
CTRL+U	Deselect all entries	Select > None
CTRL+X	Exclude selected entries	Entry > Exclude
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo in main window

2.5 Building a Structure

After you start Maestro, the first task is usually to create or import a structure. You can open existing Maestro projects or import structures from other sources to obtain a structure, or you can build your own. To open the Build panel, do one of the following:

- Click the Open/Close Build panel button in the toolbar:

- Choose Build from the Edit menu.
- Press CTRL+B.

The Build panel allows you to create structures by drawing or placing atoms or fragments in the Workspace and connecting them into a larger structure, to adjust atom positions and bond orders, and to change atom properties. This panel contains a toolbar and three folders.

2.5.1 Placing and Connecting Fragments

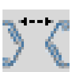
The Build panel provides several tools for creating structures in the Workspace. You can place and connect fragments, or you can draw a structure freehand.

To place a fragment in the Workspace:

1. Select Place.
2. Choose a fragment library from the Fragments menu.
3. Click a fragment.
4. Click in the Workspace where you want the fragment to be placed.

To connect fragments in the Workspace, do one of the following:

- Place another fragment and connect them using the Connect & Fuse panel, which you open from the Edit menu on the main menu bar or with the Display Connect & Fuse panel on the Build toolbar.



- Replace one or more atoms in the existing fragment with another fragment by selecting a fragment and clicking in the Workspace on the main atom to be replaced.
- Grow another fragment by selecting Grow in the Build panel and clicking the fragment you want to add in the Fragments folder.

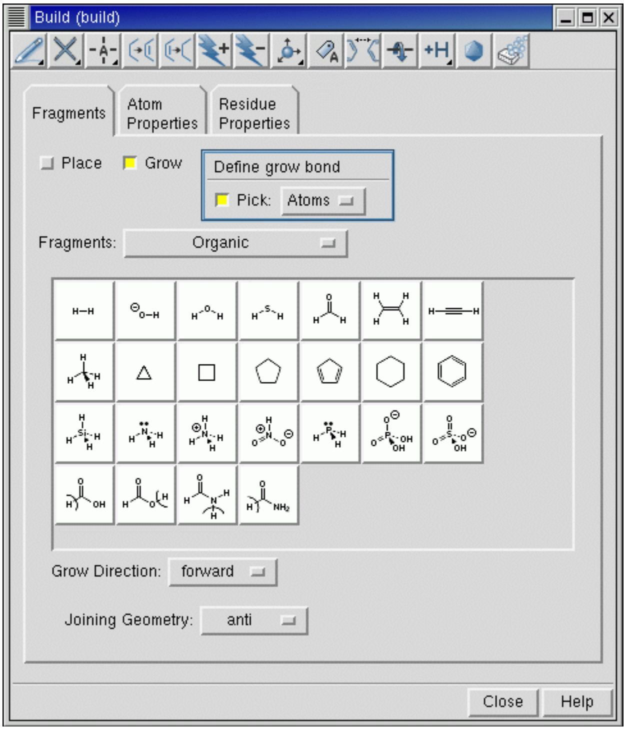
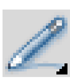


Figure 2.4. The* Build *panel.

Grow mode uses predefined rules to connect a fragment to the *grow bond*. The grow bond is marked by a green arrow. The new fragment replaces the atom at the head of the arrow on the grow bond and all atoms attached to it. To change the grow bond, choose Bonds from the Pick option menu in the Build panel and click on the desired grow bond in the Workspace. The arrow points to the atom nearest to where you clicked.

To draw a structure freehand:

1. Choose an element from the Draw button menu on the Build panel toolbar:



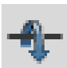
2. Click in the Workspace to place an atom of that element.
3. Click again to place another atom and connect it to the previous atom.
4. Continue this process until you have drawn the structure.
5. Click the active atom again to finish drawing.

2.5.2 Adjusting Properties

In the Atom Properties folder, you can change the properties of the atoms in the Workspace. For each item on the Property option menu—Element, Atom Type (MacroModel), Partial Charge, PDB Atom Name, Grow Name, and Atom Name—there is a set of tools you can use to change the atom properties. For example, the Element tools consist of a periodic table from which you can choose an element and select an atom to change it to an atom of the selected element.

Similarly, the Residue Properties folder provides tools for changing the properties of residues: the Residue Number, the Residue Name, and the Chain Name.

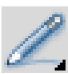
To adjust bond lengths, bond angles, dihedral angles, and chiralities during or after building a structure, use the Adjust distances, angles or dihedrals button on the main toolbar:



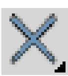
You can also open the Adjust panel from this button menu, from the Display Adjust panel button on the Build panel toolbar (which has the same appearance as the above button) or from the Edit menu in the main window.

2.5.3 The Build Panel Toolbar

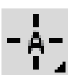
The toolbar of the Build panel provides quick access to tools for drawing and modifying structures and labeling atoms. See Section 2.3.2 on page 9 for a description of the types of toolbar buttons. The toolbar buttons and their use are described below.



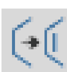
Free-hand drawing
Choose an element for drawing structures freehand in the Workspace (default C). Each click in the Workspace places an atom and connects it to the previous atom.



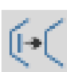
Delete
Choose an object for deleting. Same as the Delete button on the main toolbar, see page 10.



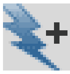
Set element
Choose an element for changing atoms in the Workspace (default C). Click an atom to change it to the selected element.



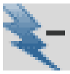
Increment bond order
Select a bond to increase its bond order by one, to a maximum of 3.



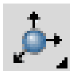
Decrement bond order
Select a bond to decrease its bond order by one, to a minimum of 0.



Increment formal charge
Select an atom to increase its formal charge by one.

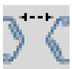


Decrement formal charge
Select an atom to decrease its formal charge by one.

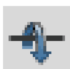


Move
Choose a direction for moving atoms, then click the atom to be moved. Moves in the XY plane are made by clicking the new location. Moves in the Z direction are made in 0.5 Å increments.

Label
Apply heteroatom labels as you build a structure. The label consists of the element name and formal charge, and is applied to atoms other than C and H.



Display Connect & Fuse panel
Open the Connect & Fuse panel so you can connect structures (create bonds between structures) or fuse structures (replace atoms of one structure with those of another).



Display Adjust panel
Open the Adjust panel so you can change bond lengths, bond angles, dihedral angles, or atom chiralities.

Add hydrogens
Choose an atom type for applying the current hydrogen treatment. Same as the Add hydrogens button on the main toolbar, see page 10.

Geometry Symmetrizer
Open the Geometry Symmetrizer panel for symmetrizing the geometry of the structure in the Workspace.

Geometry Cleanup
Clean up the geometry of the structure in the Workspace.

2.6 Selecting Atoms

Maestro has a powerful set of tools for selecting atoms in a structure: toolbar buttons, picking tools in panels, and the Atom Selection dialog box. These tools allow you to select atoms in two ways:

- Select atoms first and apply an action to them
- Choose an action first and then select atoms for that action

2.6.1 Toolbar Buttons

The small triangle in the lower right corner of a toolbar button indicates that the button contains a menu. Many of these buttons allow you to choose an object type for selecting: choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

For example, to select atoms with the Workspace selection toolbar button:

1. Choose Residues from the Workspace selection button menu:

   The button changes to:

2. Click on an atom in a residue in the Workspace to select all the atoms in that residue.

2.6.2 Picking Tools

The picking tools are embedded in each panel in which you need to select atoms to apply an operation. The picking tools in a panel can include one or more of the following:

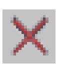
- Pick option menu—Allows you to choose an object type. Depending on the operation to be performed, you can choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The Pick option menu varies from panel to panel, because not all object types are appropriate for a given operation. For example, some panels have only Atoms and Bonds in the Pick option menu.

- All button—Performs the action on all atoms in the Workspace.
- Selection button—Performs the action on any atoms already selected in the Workspace.
- Previous button—Performs the action on the most recent atom selection defined in the Atom Selection dialog box.
- Select button—Opens the Atom Selection dialog box.
- ASL text box—Allows you to type in an ASL expression for selecting atoms.

  ASL stands for Atom Specification Language, and is described in detail in the *Maestro Command Reference Manual*.

- Clear button—Clears the current selection

- Show markers option—Marks the selected atoms in the Workspace.

For example, to label atoms with the Label Atoms panel:

1. Choose Atom Labels from the Display menu.
2. In the Composition folder, select Element and Atom Number.
3. In the picking tools section at the top of the panel, you could do one of the following:
    - Click Selection to apply labels to the atoms already selected in the Workspace (from the previous example).
    - Choose Residues from the Pick option menu and click on an atom in a different residue to label all the atoms in that residue.

2.6.3 The Atom Selection Dialog Box

If you wish to select atoms based on more complex criteria, you can use the Atom Selection dialog box. To open this dialog box, choose Select from a button menu or click the Select button in a panel. See Section 5.3 of the *Maestro User Manual* for detailed instructions on how to use the Atom Selection dialog box.

2.7 Scripting in Maestro

Although you can perform nearly all Maestro-supported operations through menus and panels, you can also perform operations using Maestro commands, or compilations of these commands, called *scripts*. Scripts can be used to automate lengthy procedures or repetitive tasks and can be created in several ways. These are summarized below.

2.7.1 Python Scripts

Python is a full-featured scripting language that has been embedded in Maestro to extend its scripting facilities. The Python capabilities within Maestro include access to Maestro functionality for dealing with chemical structures, projects, and Maestro files.

The two main Python commands used in Maestro are:

- `pythonrun`—executes a Python module. (You can also use the alias `pyrun`.) The syntax is:

    `pythonrun` *module.function*

- `pythonimport`—rereads a Python file so that the next time you use the `pythonrun` command, it uses the updated version of the module. (You can also use the alias `pyimp`.)

From the Maestro Scripts menu you can install, manage, and run Python scripts. For more information on the Scripts menu, see Section 13.1 of the *Maestro User Manual*.

For more information on using Python with Maestro, see *Scripting with Python*.

2.7.2 Command Scripts

All Maestro commands are logged and displayed in the Command Script Editor panel. This means you can create a command script by performing the operations with the GUI controls, copying the logged commands from the Command History list into the Script text area of the panel, then saving the list of copied commands as a script.

To run an existing command script:

1. Open the Command Script Editor panel from the Edit menu in the main window.
2. Click Open Local and navigate to the directory containing the desired script.
3. Select a script in the Files list and click Open.

   The script is loaded into the Script window of the Command Script Editor panel.
4. Click Run Script.

Command scripts cannot be used for Prime operations.

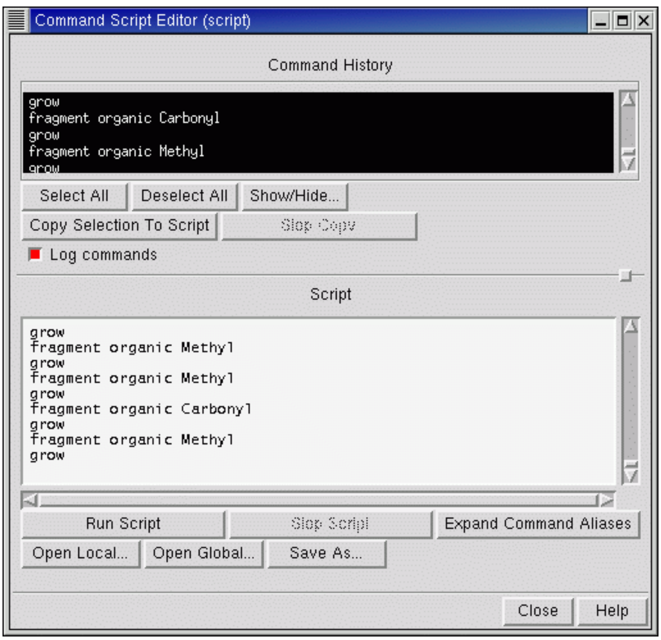


Figure 2.5. The Command Script Editor ***panel.***

2.7.3 Macros

There are two kinds of macros you can create: named macros and macros assigned to function keys F1 through F12.

To create and run a named macro:

1. Open the Macros panel from the Edit menu in the main window.
2. Click New, enter a name for the macro, and click OK.
3. In the Definition text box, type the commands for the macro.
4. Click Update to update the macro definition.
5. To run the macro, enter the following in the command input area in the main window:

   `macrorun` *macro-name*

   If the command input area is not visible, choose Command Input Area from the Display menu.

To create and run a function key macro:

1. Open the Function Key Macros panel from the Edit menu in the main window.
2. From the Macro Key option, select a function key (F1 through F12) to which to assign the macro.
3. In the text box, type the commands for the macro.
4. Click Run to test the macro or click Save to save it.
5. To run the macro from the main window, press the assigned function key.

For more information on macros, see Section 13.5 of the *Maestro User Manual*.

2.8 Specifying a Maestro Working Directory

When you use Maestro to launch Glide jobs, Maestro writes job output to the directory specified in the Directory folder of the Preferences panel. By default, this directory (the file I/O directory) is the directory from which you started Maestro.

To change the Maestro working directory:

1. Open the Preferences panel from the Maestro menu.
2. Click the Directory tab.
3. Select the directory you want to use for reading and writing files.

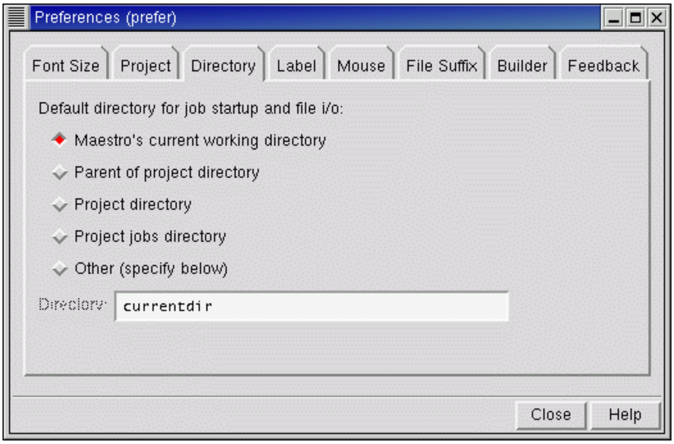


Figure 2.6. The Directory ***folder of the*** Preferences ***panel.***

You can also set other preferences in the Preferences panel. See Section 12.2 of the *Maestro User Manual* for details.

2.9 Undoing an Operation

To undo a single operation, click the Undo button in the toolbar, choose Undo from the Edit menu, or press CTRL+Z. The word Undo in the menu is followed by text that describes the operation to undo. Not all operations can be undone: for example, global rotations and translations are not undoable operations. For such operations you can use the Save view and Restore view buttons in the toolbar, which save and restore a molecular orientation.

2.10 Running and Monitoring Jobs

Maestro has panels for each product for preparing and submitting jobs. To use these panels, choose the appropriate product and task from the Applications menu and its submenus. Set the appropriate options in the panel, then click Start to open the Start dialog box and set options for running the job. For a complete description of the Start dialog box associated with your computational program, see your product's User Manual. When you have finished setting the options, click Start to launch the job and open the Monitor panel.

The Monitor panel is the control panel for monitoring the progress of jobs and for pausing, resuming, or killing jobs. All jobs that belong to you can be displayed in the Monitor panel, whether or not they were started from Maestro. Subjobs are indented under their parent in the job list. The text pane shows output information from the monitored job, such as the contents of the log file. The Monitor panel opens automatically when you start a job. If it is not open, you can open it by choosing Monitor from the Applications menu in the Maestro main window.

While jobs are running, the Detach, Pause, Resume, Stop, Kill, and Update buttons are active. When there are no jobs currently running, only the Monitor and Delete buttons are active. These buttons act on the selected job. By default, only jobs started from the current project are shown. To show other jobs, deselect Show jobs from current project only.

When a monitored job ends, the results are incorporated into the project according to the settings used to launch the job. If a job that is not currently being monitored ends, you can select it in the Monitor panel and click Monitor to incorporate the results. Monitored jobs are incorporated only if they are part of the current project. You can monitor jobs that are not part of the current project, but their results are not incorporated. To add their results to a project, you must open the project and import the results.

Further information on job control, including configuring your site, monitoring jobs, running jobs, and job incorporation, can be found in the *Job Control Guide* and the *Installation Guide*.

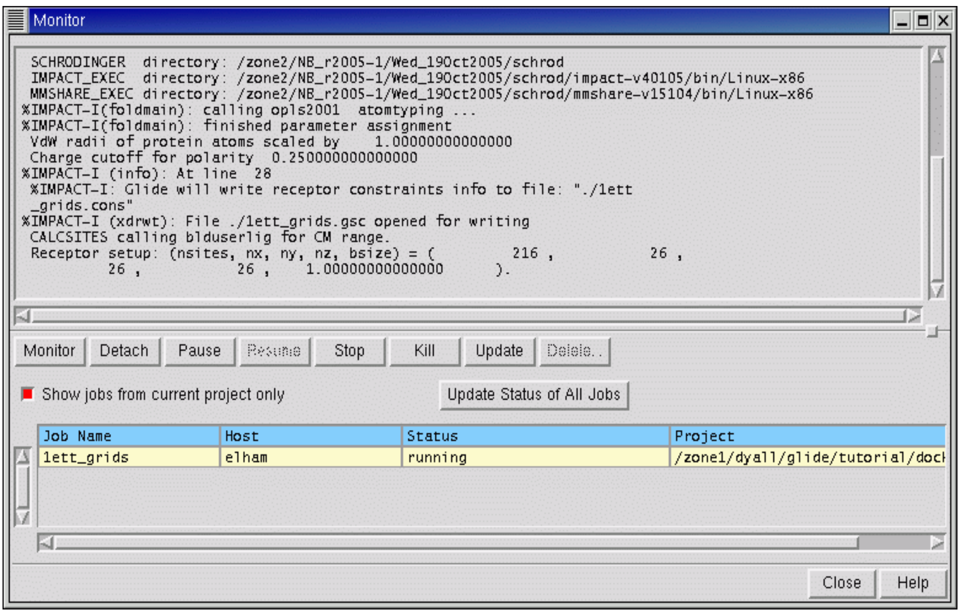


Figure 2.7. ***The*** Monitor ***panel.***

2.11 Getting Help

Maestro comes with automatic, context-sensitive help (Auto-Help), Balloon Help (tooltips), an online help facility, and a user manual. To get help, follow the steps below:

- Check the Auto-Help text box at the bottom of the main window. If help is available for the task you are performing, it is automatically displayed there. It describes what actions are needed to perform the task.
- If your question concerns a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- If you do not find the help you need using either of the steps above, click the Help button in the lower right corner of the appropriate panel. The Help panel is displayed with a relevant help topic.
- For help with a concept or action not associated with a panel, open the Help panel from the Help menu or press CTRL+H.

If you do not find the information you need in the Maestro help system, check the following sources:

- The *Maestro User Manual*
- The Frequently Asked Questions page on the Schrödinger Support Center.

You can also contact Schrödinger by e-mail or phone for help:

- E-mail: help@schrodinger.com
- Phone: (503) 299-1150

2.12 Ending a Maestro Session

To end a Maestro session, choose Quit from the Maestro menu. To save a log file with a record of all operations performed in the current session, click Quit, save log file in the Quit panel. This information can be useful to Schrödinger support staff when responding to any problem you report.

Glide Overview

This chapter contains a brief introduction to the Glide (Grid-based Ligand Docking with Energetics) program, its scientific methods and computational procedures.

Glide searches for favorable interactions between one or more typically small ligand molecules and a typically larger receptor molecule, usually a protein. Each ligand must be a single molecule, while the receptor may include more than one molecule, e.g., a protein and a cofactor. Glide can be run in rigid or flexible docking modes; the latter automatically generates conformations for each input ligand. The combination of position and orientation of a ligand relative to the receptor, along with its conformation in flexible docking, is referred to as a *ligand pose*.

The ligand poses that Glide generates pass through a series of hierarchical filters that evaluate the ligand's interaction with the receptor. The initial filters test the spatial fit of the ligand to the defined active site, and examine the complementarity of ligand-receptor interactions using a grid-based method patterned after the empirical ChemScore function (Eldridge et al., *J. Comput. Aided Mol. Des.* **1997**, *11*, 425–445).

Poses that pass these initial screens enter the final stage of the algorithm, which involves evaluation and minimization of a grid approximation to the OPLS-AA nonbonded ligand-receptor interaction energy.

Final scoring is then carried out on the energy-minimized poses. By default, Schrödinger's proprietary GlideScore multi-ligand scoring function is used to score the poses. If GlideScore was selected as the scoring function, a composite *Emodel* score is then used to rank the poses of each ligand and to select the poses to be reported to the user. Emodel combines GlideScore, the nonbonded interaction energy, and, for flexible docking, the excess internal energy of the generated ligand conformation.

3.1 Using Glide

The Glide task most frequently performed is ligand docking. The grid files produced by a single receptor grid generation task can be used for any number of jobs docking ligands to that receptor. Before generating receptor grids, it is strongly recommended that you prepare the protein. Therefore, the first steps of a typical project beginning with an unprepared protein-ligand complex structure (e.g., from PDB) might proceed using the Glide panels as follows:

1. After correcting formal charges and bond orders in the ligand, cofactors, and nonstandard residues, set up and start the automated preparation and refinement portions of the protein preparation procedure using the Protein Preparation panel. Details of protein preparation are given in Chapter 4.
2. Ensure that the ligands to be docked are in the right form. Details of this process are given in Chapter 5.
3. With the prepared receptor-ligand complex in the Workspace, use the Receptor Grid Generation panel to specify settings, optionally define Glide constraints, and start the receptor grid generation job. Details of setting up receptor grid generation jobs are given in Chapter 6.
4. Specify the base name for the receptor grid files you want to use in the Ligand Docking panel, and use the other settings and options in the panel to set up and start a ligand docking job. As many docking jobs as you want can be set up in this panel, using the current receptor grids or specifying a different set of grids to use. Details of setting up ligand docking jobs are given in Chapter 7.

Much of the information in these chapters is available in the Maestro online help. For a tutorial on using Glide, see the *Glide Quick Start Guide*.

3.2 Introduction to Glide

Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active-site region of the receptor. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses.

Conformational flexibility is handled in Glide via an extensive conformational search, augmented by a heuristic screen that rapidly eliminates conformations deemed unsuitable for binding to a receptor, such as conformations that have long-range internal hydrogen bonds. As illustrated in Figure 3.1, each ligand is divided into a *core* region and some number of *rotamer groups*. Each rotamer group is attached to the core by a rotatable bond, but does not contain additional rotatable bonds. The core is what remains when each terminus of the ligand is severed at the “last” rotatable bond. Carbon and nitrogen end groups terminated with hydrogen (—CH_3, —NH_2, —NH_3^+) are not considered rotatable because their conformational variation is of little significance. In Figure 3.1, the four central torsions are part of the core, and the methyl groups are not considered rotatable.

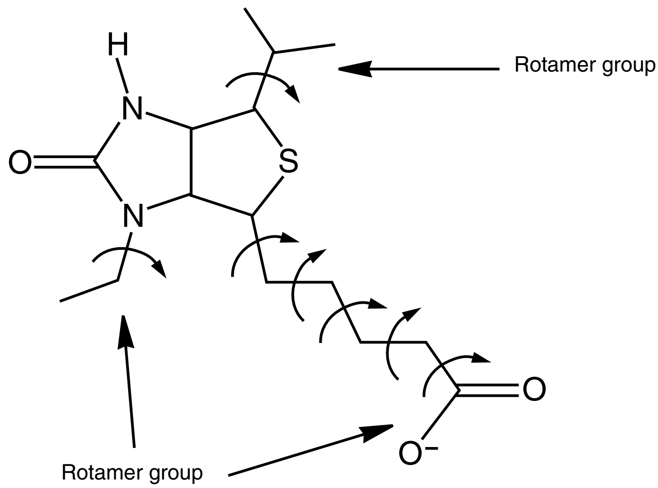


Figure 3.1. Definition of core and rotamer groups.

During conformation generation, each core region is represented by a set of core conformations, the number of which depends on the number of rotatable bonds, conformationally labile 5– and 6–membered rings, and asymmetric pyramidal trigonal nitrogen centers in the core. This set typically contains fewer than 500 core conformations, even for quite large and flexible ligands, and far fewer for more rigid ligands. Every rotamer state for each rotamer group attached to the core is enumerated. The core plus all possible rotamer-group conformations is docked as a single object. Glide can also dock sets of pre-computed conformations. However, Glide offers its greatest value when flexible docking is used to generate conformations internally.

For each core conformation (or for rigid docking, each ligand), an exhaustive search of possible locations and orientations is performed over the active site of the protein. The search begins with the selection of "site points" on an equally spaced 2 Å grid that permeates the active-site region (Stage 1 in Figure 3.2). To make this selection, pre-computed distances from the site point to the receptor surface, evaluated at a series of pre-specified directions and binned in 1 Å ranges, are compared to binned distances from the ligand center (the midpoint of the two most widely separated atoms) to the ligand surface. Glide positions the ligand center at the site point if there is a good enough match, but skips over the site point if there is not.

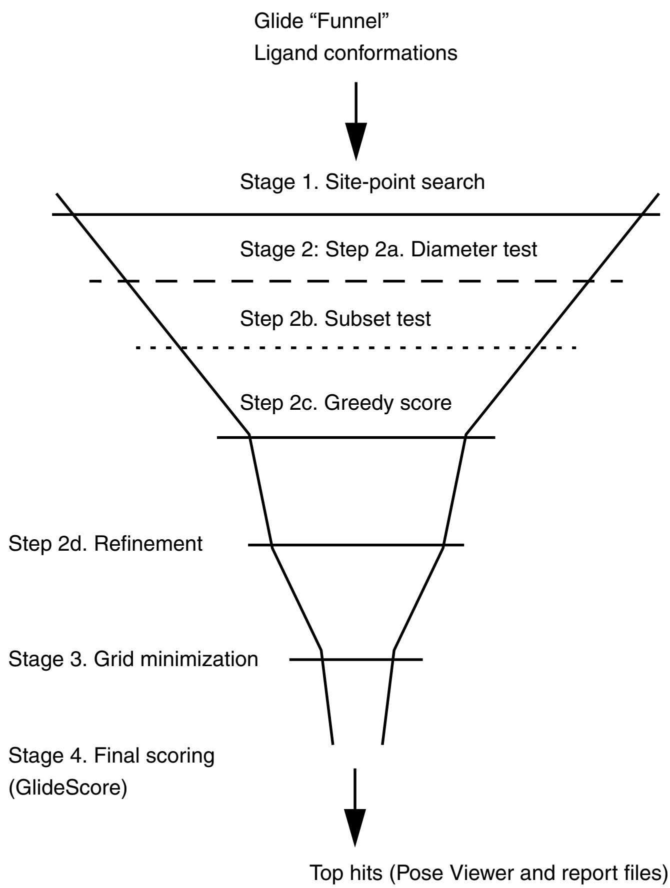


Figure 3.2. The Glide docking hierarchy.

The second stage of the hierarchy begins by examining the placement of atoms that lie within a specified distance of the line drawn between the most widely separated atoms (the *ligand diameter*). This is done for a pre-specified selection of possible orientations of the ligand diameter (Step 2a). If there are too many steric clashes with the receptor, the orientation is skipped. Next (Step 2b), rotation about the ligand diameter is considered, and the interactions of a subset consisting of all atoms capable of making hydrogen bonds or ligand-metal interactions with the receptor are scored (*subset test*). If this score is good enough, all interactions with the receptor are scored (Step 2c). The scoring in these three tests is carried out using Schrödinger's discretized version of the ChemScore empirical scoring function (Eldridge et al., *J. Comput. Aided Mol. Des.* **1997,** *11,* 425-445). Much as for ChemScore itself, this algorithm recognizes favorable hydrophobic, hydrogen-bonding, and metal-ligation interactions, and penalizes steric clashes. This stage is called "greedy scoring," because the actual score for each atom depends not only on its position relative to the receptor but also on the best possible score it could get by moving ±1 Å in *x*, *y*, or *z*. This is done to mute the sting of the large 2 Å jumps in the site-point/ligand-center positions. The final step in Stage 2 is to re-score the top greedy-scoring poses via a "refinement" procedure (Step 2d), in which the ligand as a whole is allowed to move rigidly by ±1 Å in the Cartesian directions.

Only a small number of the best refined poses (typically 100-400) are passed on to the third stage in the hierarchy—energy minimization on the pre-computed OPLS-AA van der Waals and electrostatic grids for the receptor. The energy minimization typically begins on a set of van der Waals and electrostatic grids that have been "smoothed" to reduce the large energy and gradient terms that result from too-close interatomic contacts. It finishes on the full-scale OPLS-AA nonbonded energy surface ("annealing"). This energy minimization consists only of rigid-body translations and rotations when external conformations are docked. When conformations are generated internally, however, the optimization also includes torsional motion about the core and end-group rotatable bonds. Unless otherwise specified, a small number of the top-ranked poses are then subjected to a Monte-Carlo procedure in which alternative local-minima core and rotamer-group torsion angles are examined to try to improve the energy score.

Finally, the minimized poses are re-scored using Schrödinger's proprietary *GlideScore* scoring function. GlideScore is based on ChemScore, but includes a steric-clash term and adds buried polar terms devised by Schrödinger to penalize electrostatic mismatches. The choice of best-docked structure for each ligand is made using a model energy score (*Emodel*) that combines the energy grid score, the binding affinity predicted by GlideScore, and (for flexible docking) the internal strain energy for the model potential used to direct the conformational-search algorithm. Glide also computes a specially constructed Coulomb-van der Waals interaction-energy score that is formulated to avoid overly rewarding charge-charge interactions at the expense of charge-dipole and dipole-dipole interactions. This score is intended to be more suitable for comparing the binding affinities of different ligands than is the "raw" Coulomb-van der Waals interaction energy. In the final data work-up, you can combine the computed GlideScore and "modified" Coulomb-van der Waals score values to give a composite score that usually helps improve enrichment factors in database screening applications.

This hierarchical search gives Glide exceptionally high accuracy in predicting the binding mode of the ligand. At the same time, the computational cost is dramatically reduced compared to what would be required for a complete systematic search. The key to this reduction is that the algorithm allows the rotamer groups to be optimized one at a time for a given core conformation and location of the ligand. For example, if there are five rotamer groups and each has three rotamer states, the total number of conformers in the ensemble based on this core conformation/location is $3^5 = 243$. However, if the rotamer groups are optimized one at a time, the number of conformational combinations is only 3×5 = 15, for a savings of about a factor of 15 in computational effort. While many other time-saving algorithms in Glide contribute to its performance advantages, this fundamental qualitative feature allows large libraries to be screened at an affordable computational cost.

3.3 Glide Constraints

A *Glide constraint* is a ligand-receptor interaction requirement. To use Glide constraints, you must specify receptor sites for possible ligand interactions when you set up a receptor grid generation job. When you run a ligand docking job, you can select Glide constraints to apply from the list of receptor constraint sites that you defined for the receptor.

In Glide constraint docking jobs, Glide incorporates satisfaction of these constraints into several of its hierarchical filters, allowing prompt rejection of docked poses that fail to meet the requirements.

For information on using Glide constraints, see Section 6.4 and Section 7.4.

3.4 Glide Extra-Precision Mode

The extra-precision (XP) mode of Glide combines a powerful sampling protocol with the use of a custom scoring function designed to identify ligand poses that would be expected to have unfavorable energies, based on well-known principles of physical chemistry. The presumption is that only active compounds will have available poses that avoid these penalties while at the same time securing a favorable scoring from the terms in the scoring function that reward hydrophobic contact between the protein and the ligand, appropriate hydrogen-bonding interactions, and so on. The chief purposes of the XP method are to weed out false positives and to provide a better correlation between good poses and good scores.

Extra-precision mode is a refinement tool designed for use only on good ligand poses. The more extensive XP docking method and specialized XP scoring method are strongly coupled: the more precise poses produced by XP docking are necessary for the more demanding XP scoring method. Because XP docking mode requires more CPU time, you should screen large sets of ligands first in standard-precision (SP) mode. Only the top-scoring ligands should be docked using XP mode.

Note: If the active site of the complex contains a metal, XP mode should not be used.

For information on using XP mode, see Section 7.2.

3.5 Glide/Prime Induced Fit Docking

Glide docking uses the assumption of a rigid receptor, although scaling of van der Waals radii of nonpolar atoms, which decreases penalties for close contacts, can be used to model a slight “give” in the receptor and/or ligand. This may not be sufficient to treat systems where ligand binding induces substantial conformation changes in the receptor (“induced fit.”) Schrödinger has developed a procedure for such cases which uses Prime and Glide to perform induced fit docking. For more information about Schrödinger’s Induced Fit Docking protocol, see the document *Induced Fit Docking*.

Protein Preparation

Because the quality of results depends on reasonable starting structures, Schrödinger offers a comprehensive protein preparation facility designed to ensure chemical correctness and to optimize protein structures for use with Glide. It is strongly recommended that you process protein structures with the preparation facility in order to achieve best results.

This chapter describes the preparation of protein-ligand complexes. Several preparation tasks must be performed manually before using the protein preparation facility for the automated tasks. Most of the features of the facility are available from the Protein Preparation panel. Additional features are available in the command-line application `protprep`. The utilities `pprep` and `impref` are also available. Use of the command-line application and utilities is summarized in Section 8.3 on page 114.

4.1 The Protein Preparation Facility

The protein preparation facility performs the final stages of the preparation of proteins for use in Glide, CombiGlide, QSite, and Liaison. A typical PDB structure file consists only of heavy atoms; therefore, hydrogens have to be added prior to use in Glide calculations, which use an all-atom force field. The charge state of protein residues is also important to the results generated by Glide. Before you can run a protein preparation job, you must perform some preliminary preparation tasks that are not automated.

The protein preparation facility consists of two components, *preparation* and *refinement*. After ensuring chemical correctness, the *preparation* component adds hydrogens and neutralizes side chains that are not close to the binding cavity and do not participate in salt bridges. The *refinement* component performs a restrained Impact minimization of the cocrystallized complex, which reorients side-chain hydroxyl groups and alleviates potential steric clashes. The Protein Preparation panel is used to set up jobs that perform these tasks.

If you are familiar with Maestro, or if you have followed Schrödinger's protein preparation procedure before, you might need to follow only the overview provided in Section 4.2. The steps are described in detail in later sections of this chapter. For a tutorial on protein preparation, see Chapter 3 of the *Glide Quick Start Guide*.

4.2 Step-by-Step Overview

This section provides an overview of the protein preparation process. The procedure described assumes that the initial protein structure is in a PDB-format file, includes a cocrystallized ligand, and does not include explicit hydrogens. For best results, structures with missing residues near the active site should be repaired before protein preparation. After processing with Schrödinger's protein preparation facility, you will have files containing refined, hydrogenated structures of the ligand and the ligand-receptor complex. The prepared structures are suitable for use with Glide. In most cases, not all of the steps outlined need to be performed. See the descriptions of each step to determine whether it is required.

1. Import a ligand/protein cocrystallized structure, typically from PDB, into Maestro. The preparation component of the protein preparation facility requires an identified ligand.
2. Locate any waters you want to keep, then delete all others.

   These waters are identified by the oxygen atom, and usually do not have hydrogens attached. Generally, all waters (except those coordinated to metals) are deleted, but waters that bridge between the ligand and the protein are sometimes retained. If any waters are kept, hydrogens will be added to them by the preparation component of the protein preparation job. Afterwards, it is useful to check that these water molecules are correctly oriented.
3. Simplify multimeric complexes.
   - Determine whether the protein-ligand complex is a dimer or other multimer containing duplicate binding sites and duplicate chains that are redundant.
   - If the structure is a multimer with duplicate binding sites, remove redundant binding sites and the associated duplicate chains by picking and deleting molecules or chains in Maestro.
4. Adjust the protein, metal ions, and cofactors.
   - Fix any serious errors in the protein. Incomplete residues are the most common errors, but are relatively harmless if they are distant from the active site. Structures that are missing residues near the active site should be repaired.
   - Check the protein structure for metal ions and cofactors.
   - If there are bonds to metal ions, delete the bonds, then adjust the formal charges of the atoms that were attached to the metal as well as the metal itself.
   - Set charges and correct atom types for any metal atoms, as needed.
   - Set bond orders and formal charges for any cofactors, as needed.

5. Adjust the ligand bond orders and formal charges.

   If you are working with a dimeric or large protein and two ligands exist in two active sites, the bond orders have to be corrected in both ligand structures.

6. Run protein preparation.

   - Open the Protein Preparation panel, define the ligand by picking, select the desired Procedure, set other options as necessary, and click Start.

     The Protein Preparation Start dialog box opens.

   - Type the name of your job in the Name text box, and click Start.

7. Review the prepared structures.

   - If problems arise during the preparation or refinement stages, review the log file, correct the problems, and rerun.
   - Examine the refined ligand/protein/water structure for correct formal charges and protonation states resulting from Step 6 and make final adjustments as needed.

4.3 Importing the Protein Complex Structure

This step begins the protein preparation procedure.

To import a ligand-receptor protein complex structure into Maestro:

1. On the toolbar, click the Import structures button:

   The Import panel is displayed.

2. Select PDB format.

3. Enter the name of the file, or select the file in the Files list.

4. Click Import.

5. To display the Project Table, click the Open/Close project table button on the toolbar:

The imported entry is highlighted in the Project Table and displayed in the Workspace.

4.4 Deleting Unwanted Waters

Water molecules in the crystallographic complex are generally not used unless they are judged critical to the functioning of the protein–ligand interaction. When waters are used, they are later included in the protein as “structural” waters.

Deleting all waters to make a site more accessible might be desirable in a Glide project. For example, retaining the water under the flap in 1HPX would prevent the docking of the DuPont-Merck cyclic urea that displaces this water. In other cases, removing waters might enable you to find ligands capable of “replacing” the missing waters. An alternative approach for 1HPX would be to prepare versions of the protein with and without the flap water and to dock ligands against both. In our database screens for 1HPX, excellent rank orders were found for the known ligands, even though the flap water was removed.

If you know there are no waters that are important to the protein-ligand interaction, skip to Section 4.4.2 to delete all waters.

4.4.1 Locating Structural Waters

Structural waters can be located by displaying atoms within a certain distance of the ligand.

To locate structural waters in the protein structure:

1. Choose Molecule Number from the Color all atoms by scheme button menu.

   The ligand should be clearly distinguishable. The water molecules are represented only by the oxygen atoms, because a united-atom atom type is in use.

2. Choose Molecule from the Display only selected atoms button menu.

3. Click on an atom in the ligand.

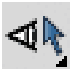
   The ligand is displayed and all other atoms are undisplayed.

4. Choose a distance, such as 5 Å, from the Display residues within N Å of currently displayed atoms toolbar button menu.

The ligand plus all atoms (including water oxygens) within the chosen distance of the ligand are now displayed.

5. Choose Select from the Draw atoms in Ball & Stick button menu.

   The Atom Selection dialog box opens.

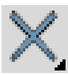
6. In the Residue tab, select Residue Type.

7. Select the water residue type, HOH, click Add, then click OK.

   The water oxygens, assuming no hydrogens have been added, are displayed in Ball & Stick representation as balls.

4.4.2 Deleting All Water Molecules

If you decide to delete all waters, choose Waters from the Delete button menu on the toolbar.

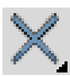


All water molecules are deleted. Skip to Section 4.5.

4.4.3 Deleting Distant Water Molecules

If you want to keep one or more waters, begin by removing those that are farther than a specified distance from the ligand.

1. Choose Select from the Delete button menu on the toolbar.

   The Atom Selection dialog box opens.

2. In the Molecule tab, choose Molecule Number and enter the ligand's molecule number. Click Add.

3. Click the Proximity button. In the Proximity dialog box:

   a. Select Beyond, enter a distance in the text box, and select Angstroms.

   b. Under Fill, select Residues and Exclude source.

      This keeps the ligand itself from being deleted.

   c. Click OK to exit the Proximity dialog box.

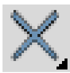
4. In the Residue tab, choose Residue Type, and select HOH.
5. Click Intersect.

   Most of the water oxygens are marked in the Workspace.
6. Click OK to delete the selected water molecules.

4.4.4 Deleting Remaining Unwanted Waters

After deleting water molecules beyond a certain distance from the ligand, examine the Workspace and delete any remaining water molecules you do not want to keep:

1. On the toolbar, choose Molecules from the Delete button menu:

   
2. Click on a water oxygen to delete that water molecule.

   When you have removed all but the desired waters, continue with Section 4.5.

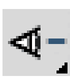
4.5 Simplifying the Protein Complex

4.5.1 Determining Whether the Complex Is a Multimer

To determine whether the ligand-receptor complex is a multimer, compare the chains that appear in the sequence viewer. If there are two or more chains with identical sequences, the complex may be a multimer. If this is the case, there may be duplicate copies of the binding site of interest, with duplicate chains forming the duplicate binding sites.

If the binding interaction of interest takes place within a single subunit, you should retain only one ligand-receptor subunit to prepare for Glide. However, if two identical chains are both required to form the active site, neither should be deleted. To see whether two duplicate chains are involved with the active site, undisplay the protein's amino acid residues:

1. Choose Protein Backbone from the Undisplay button menu.

   
2. Choose Protein Side Chains from the Undisplay button menu.

Ligands, cofactors, metal ions, and water oxygens remain visible. If two or more identical ligands or ligand/cofactor groups are present, then the complex is most likely a multimer, and the redundant groups and the duplicate chains associated with them can be deleted.

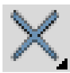
4.5.2 Retaining Needed Subunits

If the protein complex structure is a multimer with duplicate binding sites, it can be truncated by deleting all but a single ligand binding site and the associated receptor subunits. If you choose not to truncate the structure, skip to Section 4.6 on page 46. The process below assumes that the protein is initially not displayed.

To remove redundant subunits or receptor sites of a multimer:

1. Delete all but one ligand or ligand/cofactor pairing:

   a. Choose Molecules from the Delete button menu.

   b. Click on any atom in a molecule to delete that molecule.

2. Display the ligand or ligand/cofactor pair in CPK:

   a. Choose Molecules from the Draw atoms in CPK button menu:

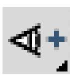
   b. Click on an atom in the ligand to display it in CPK.

   c. If there is a cofactor, click on an atom in that molecule as well.

   d. Click the toolbar button a second time to leave the Draw atoms in CPK pick state.

3. Redisplay the protein backbone:

   Choose Protein Backbone from the Also display button menu.

   Making just the backbone visible will provide enough information without unduly cluttering the Workspace.

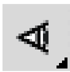
4. Assign coloring by Chain Name:

   Choose Chain Name from the Color all atoms by scheme button menu.

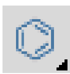
5. Delete duplicate protein chains:
   a. Choose Chains from the Delete button menu.
   b. Click on a backbone atom in each protein chain you want to delete.
6. Delete duplicate ligands and cofactors:
   a. Choose Molecules from the Delete button menu.
   b. Click on an atom in each ligand or cofactor to be deleted.
7. When finished, redisplay the rest of the protein:

   Choose All from the Display only button menu.

8. Put all atoms, including the ligand and any cofactors, back into wire-frame:

   Double-click the Draw bonds in wire button.

4.6 Adjusting the Protein, Metal Ions, and Cofactors

Problems originating in the PDB protein structure may need to be repaired before it can be used. Incomplete residues are the most common errors, but are relatively harmless if they are distant from the active site. Structures that are missing residues near the active site should be repaired.

If the protein already includes hydrogen atoms, you will need to decide how to proceed. If all hydrogens are present, you could use the structure as is and omit running the protein preparation procedure. This approach is not recommended unless you are absolutely satisfied that the structure is properly prepared and contains no untenable steric clashes.

Typically, you will need to perform the tasks in this section to assure that the protein structure is ready to be prepared.

4.6.1 Checking the Protein Structure for Metal Ions and Cofactors

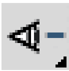
1. Ensure that the entire structure, including any metals and cofactors, is included in the Workspace.

2. Choose Element from the Color all atoms by scheme button menu.

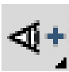
   All atoms in the Workspace are now colored by element.

3. Choose Protein Backbone from the Undisplay button menu.

4. Choose Protein Side Chains from the Undisplay button menu.

5. As needed, redisplay protein residues near a metal or cofactor, using the Also display button menu and the Atom Selection dialog box.

6. Examine the protein structure to determine how to continue.

   - If the protein contains neither metal ions nor cofactors, proceed to Section 4.7.
   - If the protein contains metal ions but no cofactors, continue with Section 4.6.2 and check metal ion properties before proceeding to Section 4.7.
   - If the protein contains cofactors but no metal ions, continue with Section 4.6.4 and check cofactor properties before proceeding to Section 4.7.
   - If the protein contains both metal ions and cofactors, do all procedures: check metal ion properties as described in Section 4.6.2, check cofactor properties as described in Section 4.6.4, then proceed to Section 4.7.

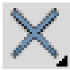
4.6.2 Deleting Protein-Metal Bonds

Metal ions in the protein complex cannot have covalent bonds to protein atoms. The preparation stage of protein preparation automatically deletes protein-metal bonds before hydrogens are added, but this can leave incorrect formal charges on the atoms that were bonded to metal, causing incorrect structures to be generated by protein preparation.

It is safest, therefore, to delete the bonds, then check and adjust element names and formal charges for both metal and non-metal atoms whose bond order you have changed. When you have run protein preparation, it is highly recommended that you examine the prepared complex for correct protonation states and charges in the active site, then make manual corrections if needed. Before running a docking job, you can run a score-in-place Glide calculation on the complex and check that the metal-ligation energy is reasonable. If it is highly positive, you may have to re-adjust the charge and protonation states in the active site manually.

To manually delete bonds between metals and protein atoms:

1. Choose Bonds from the Delete button menu.



2. Click on the bonds to be deleted.

4.6.3 Adjusting Metal Ion Charges

The MacroModel atom types for metal ions are sometimes incorrectly translated into dummy atom types (Du, Z0, or 00) when metal-protein bonds are specified in the input structure. Furthermore, isolated metal ions may erroneously be assigned general atom types (GA, GB, GC, etc.). The Protein Preparation procedure cannot treat structure files containing these atom types; they should be corrected as described in this section.

To display element labels and formal charges:

1. Open the Build panel by clicking the Open/Close build panel button.

2. In the Build panel toolbar, click the Label button.

All metal ions (and other heteroatoms) are labeled with their element symbol and formal charge.

3. Check any metal ions to make sure they are correct. If they are, the next step in the process is Section 4.6.4. If not, you can correct them.

To correct metal ion atom types:

1. In the Build panel, click the Atom Properties tab and select Atom Type (MacroModel) from the Property option menu.
2. Select the correct atom type for the metal ion from the list.

   The atom type for metal ions includes both element name and formal charge. Atom type numbers are in parentheses.
3. Click on the metal ion to be changed.

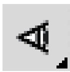
4.6.4 Displaying and Adjusting the Cofactor

Cofactors are included as part of the protein, but because they are not standard residues it is sometimes necessary to use Maestro's structure-editing capabilities to ensure that multiple bonds and formal charges are assigned correctly.

If the Build panel is not displayed, click Open/Close build panel on the main toolbar.

To display only the cofactor:

1. Choose Select from the Display only button menu.

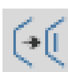
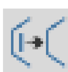
   The Atom Selection dialog box is displayed.
2. In the Residue tab, choose Residue Type.
3. Click the residue type of the cofactor, which will be near the end of the list.

   The cofactor is highlighted.
4. Click Add, then click OK.

The cofactor is displayed. Because the cofactor was chosen by residue type and not molecule number, this method works even if the cofactor is covalently bonded to another residue.

To set or change cofactor bond orders:

1. On the Build panel toolbar, click the Decrement bond order or Increment bond order button, as appropriate.

    
2. Click on bonds as necessary to set the bond order.

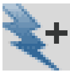
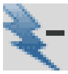
To set or correct the formal charge on any cofactor atoms:

1. On the Build panel toolbar, click the Label button.

All metal ions (and other heteroatoms) are labeled with their element symbol and formal charge.

2. On the Build panel toolbar, click on the Increment formal charge or Decrement formal charge button, as appropriate.

3. Click on an atom whose formal charge must be increased or decreased. Repeat as necessary. The atom labels show the current formal charge.

To correct the atom type of any mistyped atoms:

1. In the Atom Properties tab of the Build panel, choose Atom Type (MacroModel) from the Property option menu.
2. Select the correct atom type for the mistyped atom from the list.
3. Click on the atom to be changed.
4. If the cofactor contains any metal ions, bonds between the metal and cofactor can be removed as in Section 4.6.2.

For more information about structure editing in Maestro, click Help or see Chapter 4 of the *Maestro User Manual*.

4.7 Adjusting the Ligand

4.7.1 Adjusting Ligand Atom and Bond Properties

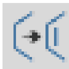
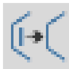
If you have not already colored by element, do so now by choosing Element from the Color all atoms by scheme button menu.

If the Build panel is not displayed, click Open/Close build panel on the main toolbar:

Most of the ligand bond orders can be fixed by choosing Assign Bond Orders from the Tools menu. After fixing the bond orders, you should go through the procedure below to fix any remaining bond order or formal charge problems.

To set or change ligand bond orders:

1. On the Build panel toolbar, click the Decrement bond order or Increment bond order button, as appropriate.

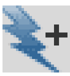
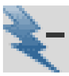
2. Click on bonds as necessary to set the bond order.

To set or change formal charges on any ligand atoms:

1. On the main toolbar, choose Formal Charge from the Label atoms button menu.

2. On the Build panel toolbar, click on the Increment formal charge or Decrement formal charge button, as appropriate:

3. Click on an atom whose formal charge must be increased or decreased. Repeat as necessary. The atom labels show the current formal charge.

To correct the atom type of any mistyped atoms:

1. On the main toolbar, choose Atom Type (MacroModel) from the Label atoms button menu:

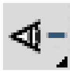
2. In the Atom Properties tab of the Build panel, choose Atom Type (MacroModel) from the Property option menu.
3. Select the correct atom type for the mistyped atom from the list.
4. Click on the atom to be changed.

4.7.2 Manually Deleting Explicit Ligand-Metal Bonds

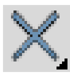
If the complex structure contains any bonds from the ligand or a cofactor to a protein metal, they must be deleted. Glide, and the OPLS-AA force field it uses, models such interactions as a van der Waals plus electrostatic interaction. Glide cannot handle normal covalent bonds to the ligand, such as might be found in an acyl enzyme.

Maestro will delete all bonds to metal atoms before the protein preparation job begins. However, if there are metal-ligand bonds, they will interfere with the identification of the ligand molecule. To avoid this, delete such bonds manually.

1. To check for ligand-metal bonds:
   a. On the toolbar, choose Protein Backbone from the Undisplay button menu:

   b. Repeat the process, choosing Protein Side Chains.
2. If any metal-ligand bonds exist, delete them:
   a. Choose Bonds from the Delete button menu on the toolbar.

   b. Click on the bonds to be deleted.
3. Redisplay the complete protein by choosing All from the Display Only button menu on the toolbar.

4.7.3 Checking for Other Protein-Ligand Bonds

If any covalent bonds exist between the protein and ligand, they will preclude treatment in Glide or Liaison. Bonds between the components of the protein/metals/cofactor structure were deleted in Section 4.6.2.

4.8 Running Protein Preparation on the Structures

From this point on, all structural manipulations are done by the Protein Preparation panel, shown in Figure 4.1, and its related scripts. Before you open this panel, ensure that the protein and ligand are in the Workspace.

To open the Protein Preparation panel, select Protein Preparation from the Glide submenu of the Applications menu on the main menu bar.

4.8.1 Defining the Ligand

Before launching a protein preparation job, you must choose a molecule in the Workspace that will be treated as the ligand. In the Protein Preparation panel, select Pick ligand, and then pick the ligand by clicking on it in the Workspace. When Show markers is selected, the ligand is highlighted with a blue-green marker. The rest of the Workspace is then treated as the protein.

4.8.2 Choosing a Procedure

The Protein Preparation panel facilitates three types of jobs: Preparation only, Refinement only, and Preparation and refinement.

The Preparation component neutralizes residues that are beyond a set distance from the ligand. The Preparation process also detects some conflicts in hydrogen bonding. It corrects them when possible, either by exchanging carbonyl and hydroxyl oxygens in a neutralized carboxylic acid group, or by creating the alternate (HIE) tautomer of a histidine side chain.

The Refinement component uses Impact to run a series of restrained, partial minimizations on the combined, hydrogenated structure. Minimizations continue until the average RMS deviation of the non-hydrogen atoms reaches the specified limit (0.3 Å by default).

The first step in the sequence of restrained minimizations reorients side-chain hydroxyls in serine, threonine, and tyrosine residues, and side-chain sulfhydryls of cysteine residues. This is accomplished by tightly tethering non-hydrogen atoms with a force constant of 10 kcal/mol·Å^2 and by minimizing the hydrogens with torsion interactions turned off.

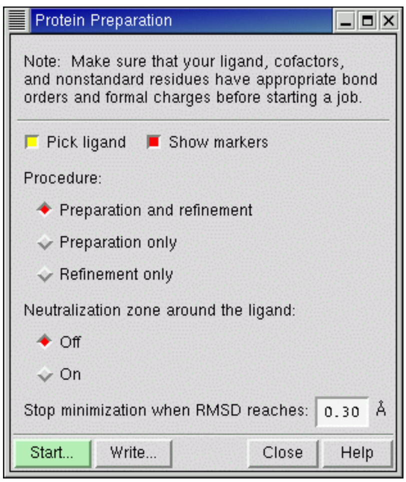


Figure 4.1. The Protein Preparation ***panel.***

Each restrained minimization employs a limited number of minimization steps and is not intended to minimize the system completely. Subsequent steps restore the torsion potential and use progressively weaker restraints on the non-hydrogen atoms (hydrogen atoms are always free). The force constants employed are 3, 1, 0.3, and 0.1 kcal/mol·$Å^2$.

Preparation and refinement, the default, runs both components. This is the recommended mode if you have not yet run any preparation jobs on the protein. Separate Preparation only and Refinement only jobs can be run if you encountered a problem in the combined Preparation and refinement job. Subsequent Refinement only jobs can be performed after a Preparation and refinement job if water molecules need to be reoriented or if other structural adjustments need to be made.

4.8.3 Other Options

1. Neutralization zone around the ligand

   The neutralization zone is 10-20 Å. You can select On to apply neutralization in this zone or Off to turn off neutralization in this zone.

2. Stop minimization when RMSD reaches: 0.30 Å

   This is the default value. It allows the refinement portion of the job to halt when the average RMSD of the heavy atoms reaches 0.30 Å.

4.8.4 Starting the Protein Preparation Job

To start the protein preparation job, click Start. The Start dialog box is displayed, in which you can select a job name and a host, and enter your user name on the host if it is different from the host on which Maestro is running.

If you decide to run preparation and refinement separately, you will need to run a Preparation only job and refine the results with a subsequent Refinement only job.

If you want to run the job from the command line, click Write to write the input files you will need without starting the job. See Section 8.3 on page 114 for information on command line options.

Click Start in the Start dialog box when you are ready to launch the job. When the job starts, the monitor panel is displayed, including the running log of the job. When the job finishes, the prepared complex is appended as a new entry to the Project Table.

4.8.5 Output Job Files

Running Preparation and refinement produces the same files as running Preparation only followed by Refinement only. The following structure files are produced, where *jobname* is the job name:

jobname`_lig.mae`	The input ligand structure file
jobname`_lig_prep.mae`	The post-preparation ligand structure file
jobname`_lig_ref.mae`	The post-refinement ligand structure file. If present, the receptor structure file contains only the receptor.
jobname`_prot.mae`	The input receptor structure file
jobname`_prot_prep.mae`	The post-preparation receptor structure file
jobname`_prot_ref.mae`	The post-refinement receptor structure file. Contains the receptor and ligand structures, unless there is a separate ligand structure file.
jobname`.log`	The log file for the complete preparation and refinement job

4.9 Checking the Output Structures

Finally, after both the preparation and refinement components have successfully run, you should check the completed ligand and protein structures.

4.9.1 Checking the Orientation of Water Molecules

Perform this step only if you identified and kept some structural waters in Section 4.4. Reorienting the hydrogens is not strictly necessary, as their orientation should have been changed during refinement in Section 4.8, but it is useful to check that the orientation is correct.

If the orientation is incorrect, reorient the molecules by using the following procedure:

1. Choose Global/Local from the Local transformation button menu.

   The Advanced Transformations panel is displayed.

2. Under Atoms For Transformation, use the picking controls to select the entire water molecule you want to reorient.

3. Under A Center For Transformation, use the picking controls to select the oxygen atom of the water molecule.
4. Under Rotation/Translation Scope, select Local.
5. Use the middle mouse button to change the orientation of the water hydrogens.
6. Close the Advanced Transformations panel.

   Transformations should now be global again.

When you have corrected the orientation of the retained water molecules, run a Refinement only job on the adjusted protein-ligand complex as described in Section 4.8.

4.9.2 Resolving H-Bonding Conflicts

One or more residues may need to be modified to resolve an acceptor-acceptor or donor-donor clash. If residues need to be modified, follow these steps:

1. Place the refined protein-ligand complex in the Workspace.
2. Examine the interaction between the ligand and the protein (and/or the cofactor).
3. Use your judgment and chemical intuition to determine which protonation state and tautomeric form the residues in question should have.
4. Use the structure-editing capabilities in Maestro to resolve the conflict.

Some of these clashes are recognized by the preparation process but cannot be resolved by it. The preparation process may have no control over other clashes. An example of the latter typically occurs in an aspartyl protease such as HIV, where both active-site aspartates are close to one or more atoms of a properly docked ligand. Because these contact distances fall within any reasonable cavity radius, the carboxylates are not subject to being neutralized and will both be represented as negatively charged by the preparation process. However, when the ligand interacts with the aspartates via a hydroxyl group or similar neutral functionality, one of the aspartates is typically modeled as neutral.

Ligand Preparation

5.1 Ligand Preparation Checklist

Chapter 4 discussed the preparation of receptor and ligand-receptor structure files for use in Glide. Candidate ligand structures must also have certain characteristics if they are to be docked using Glide. Some of these conditions can be met by using Maestro features or command-line utilities to alter the ligand structure file.

To be submitted to Glide, ligand structures:

1. Must be three-dimensional (3D).
2. Must each consist of a single molecule that has no covalent bonds to the receptor, with no accompanying fragments, such as counter-ions and solvent molecules.
3. Must be supplied in Maestro, SD, or PDF format. Maestro transparently converts SD, MacroModel, Mol2, PDB, and other formats to Maestro format during structure import. However, Glide has no direct support for other formats, so you should ensure that your structures are in Maestro, SD, or PDB format before starting Glide jobs.

   Structure file format conversion can be done from the command line with utilities such as `pdbconvert`, `sdconvert`, and `maemmod`—see Appendix D of the *Maestro User Manual*.
4. Must have all their hydrogens (filled valences). These can be added in Maestro by using either the Add hydrogens toolbar button:

   or the Hydrogen Treatment panel (select Hydrogen Treatment from the Edit menu).

   Hydrogen atoms can also be added (or removed) using the utility `applyhtreat`, which is described in Appendix D of the *Maestro User Manual*.

5.2 LigPrep

The Schrödinger ligand preparation product LigPrep is designed to prepare high quality, all-atom 3D structures for large numbers of drug-like molecules, starting with 2D or 3D structures in SD or Maestro format. LigPrep can be run from Maestro or from the command line. For detailed information on LigPrep, see the *LigPrep User Manual*.

To run LigPrep, you must have a LigPrep license. The MacroModel commands `premin` and `bmin` require LigPrep licenses when run in a LigPrep context, and are limited to a restricted set of commands when run using a LigPrep license. For information about obtaining LigPrep, contact help@schrodinger.com.

The simplest use of LigPrep produces a single low-energy 3D structure with correct chiralities for each successfully processed input structure. LigPrep can also produce a number of structures from each input structure with various ionization states, tautomers, stereochemistries, and ring conformations, and eliminate molecules using various criteria including molecular weight or specified numbers and types of functional groups present.

5.2.1 The LigPrep Process

The LigPrep process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures, and optimize the structures. Many of the steps are optional, and are controlled by selecting options in the LigPrep panel or specifying command-line options. The steps are outlined below. Each step is performed by the script or program listed in the step.

1. Convert structure format.

   If the input structure file is in SD format it is converted to Maestro format by `sdconvert`. Parities specified in the SD file are converted into chiralities, which are stored as properties in the Maestro file.

2. Select structures.

   A subset of the input structures can be selected for processing. The selection is done by `maesubset` for Maestro input files and by `sdconvert` for SD input files.

3. Add hydrogen atoms.

   Structures that have implicit hydrogen atoms may need to have hydrogen atoms added before the 3D structures can be minimized. Hydrogen atoms are added in a manner that is consistent with a particular force field. This step is performed by `applyhtreat`, which is the program used by the Hydrogen Treatment panel in Maestro.

4. Remove unwanted molecules.

   If structures have additional molecules included, such as counter ions in salts and water molecules, these may need to be removed. The `desalter` removes all but the molecule containing the most atoms from each structure.

5. Neutralize charged groups.

   Charged groups must be neutralized before ionization states can be generated. Neutral molecules are also required by various applications, such as QikProp. The neutralization is performed by `neutralizer`, which adds or removes hydrogen atoms.

6. Generate ionization states.

   For some applications it is important that all species that exist in a given pH range are available. In this step, the `ionizer` generates various ionization states for each structure. This step should be preceded by a neutralization step.

7. Generate tautomers.

   As with ionization, the significantly populated tautomers may be important for some types of calculations, such as docking with Glide. The `tautomerizer` generates various tautomers for each structure.

8. Filter structures.

   In this step, structures that match specified conditions can be removed. The condition can be on a property, such as Molecular weight > 1000, or on the structure, such as the presence or absence of a specific functional group. This step is performed by `ligparse`.

9. Generate alternative chiralities.

   2D structures do not always have complete chirality information, and it can be useful to vary the chiralities of the atoms to find all the low-energy structures or to provide a range of possible structures for investigation. This step identifies additional chiral atoms in the structures and generates additional structures with the same molecular formula but different chiral properties. The step is performed by the `stereoizer`.

10. Generate low-energy ring conformations.

    When ring conformation information is not available, it is important to generate a range of conformers so that the low-energy structures can be located. Ring confirmations are generated for each structure by `ring_conf`.

11. Remove problematic structures.

    Structures that could cause subsequent processing failures either in the energy minimization of the structures or in other applications are removed by `premin`.

12. Optimize the geometries.

    The geometries of the generated structures are optimized using a restricted version of the MacroModel computational program, `bmin`, or a short conformational search is performed to relax the structure into 3 dimensions while strongly encouraging chiral centers to adopt the proper chiralities (if the structure is highly strained).

13. Convert output file.

    If output in SD format was requested, `sdconvert` is run to perform the conversion.

5.2.2 The LigPrep Panel

The LigPrep panel allows you to set up LigPrep jobs in Maestro. Choose LigPrep from the Applications menu to open the panel. For details of panel options and operation, see Chapter 3 of the *LigPrep User Manual*.

The default options in the LigPrep panel run the `desalter`, add hydrogens, and minimize the ligand structure (performing a 2D-3D conversion, if necessary). Below are notes on panel options that produce more than one output structure per input structure.

The `stereoizer` can generate two stereoisomers per chiral center in the ligand, up to a specified maximum. There are three Stereoisomers options:

The first two options, Retain specified chiralities (the default) and Determine chiralities from 3D structure, generate both isomers only at chiral centers where chirality is unspecified or indeterminate; centers with known chirality retain that chirality.

The difference is that Retain specified chiralities takes its chirality data from the input file (SD or Maestro), while Determine chiralities from 3D structure ignores input file chiralities and takes chirality information from the 3D geometry.

Generate all combinations produces the maximum number of structures, up to the maximum, which by default is 32 stereoisomers, but can be changed using Generate stereoisomers (maximum) *max* per ligand.

The Ionization options allow you to generate all the ligand protonation states that would be found in the specified pH range. The Ionization options are:

Retain original state

Neutralize (best for QikProp)

Generate possible states at target pH *target* +/- *range*. This is the default, and can generate several different output structures for each input structure. The default pH *target* is 7.0 with a +/- *range* of 2.0, so the default pH range is 5.0 – 9.0. Both the target and range settings can be changed. You can use either the `ionizer` or Epik to generate ionization states. Epik is a separate product, so you must purchase this product to use it.

Generate low energy ring conformations: *number* per ligand. The default is to generate only the lowest energy conformation.

Desalt is selected by default.

Generate tautomers is selected by default. The `tautomerizer` generates up to 8 tautomers per ligand, selecting the most likely tautomers if more than 8 are possible. If you are comfortable that the input structures are already in the correct tautomeric form for docking to a particular target, then the `tautomerizer` should be turned off by deselecting Generate tautomers.

5.3 The Ionization State Expander (`ionizer`)

While LigPrep as a whole requires additional licenses, one LigPrep tool, the `ionizer`, is included with Glide. This section provides an introduction and usage summary for the `ionizer` as a service in Glide.

The `ionizer` generates ionization states of ligands to match the pH range and other conditions that you specify. The resulting ligands can be used as input to programs such as Glide. Starting with a Maestro-format input file of neutral molecular structures (for example, from a database), the `ionizer` produces a Maestro-format output file that has expanded to include multiple ionization states of each molecule, allowing Glide to select among them.

The `ionizer` requires the installation of a module called `services`. When you run the `INSTALL` script to install Schrödinger software, be sure to select the `services` product, which contains the `ionizer` software. For more information on installation, see the *Installation Guide*.

The `ionizer` must be run from the command line as follows:

`$SCHRODINGER/utilities/ionizer` [*options*]

The options are listed in Table 5.1.

Table 5.1. Summary of `ionizer` *options*

Option	Description
`-h|-help`	Show usage summary message.
`-doc`	Show more detailed usage message.
`-v|-ver|-version`	Show program version information.
`-j|-job|-jobname` *jobname*	Base name of job. No default (must be specified unless all essential files are specified).
`-i|-in|-infile` *infile*	Default is *jobname*`.mae`.
`-o|-out|-outfile` *outfile*	Default is *jobname*`-ion.mae`.
`-b|-bad|-badfile` *badfile*	Default is *jobname*`-ion-bad.mae`.

Table 5.1. Summary of `ionizer` *options (Continued)*

Option	Description
`-l|-log|-logfile` *logfile*	Default is *jobname*`.log`; use `-l` to log to screen.
`-ph` *value*	Effective pH of active site (default 7.0).
`-pht|-phthresh` *maxdiff*	pH difference threshold (default 2.0). For pH-based ion state rejections, where *maxdiff* is the difference limit on de/protonated |pKa-pH|.
`-pkt|-pkthresh` *maxdiff*	Strong/weak pK threshold (no default). Overrides pH-based rejection mode; reject on pKa values only (no pH), where *maxdiff* is the limit on de/protonated pKa differences.
`-mi|-maxions` *count*	Maximum number of ionizations (default 4).
`-mq|-maxabstotq` *charge*	Maximum absolute total charge (default 2).
`-mg|-maxgroups` *count*	Maximum number of ion groups to handle (default 15).
`-mo|-maxoutcts` *count*	Maximum number of output structures per input structure (default 512).
`-sm|-showmatches`	Show substructure pattern matches.
`-sf|-showfinal`	Show final ionization candidate list.
`-ll|-loglevel` *level*	Expansion report log level: Use `0` for quietest (default). Use `1` to log state generations. Use `2` to log ion fragment fusions too.
`-ss|-showskips`	Show skipped state generations. Augments log level 1 and up. Log levels > 1 give skip reasons.
`-kp|-keep_props`	Retain all properties in output CTs. Absent this option, connectivity-dependent properties are cleared
`-strict`	Terminate run if any input CT is bad. Unsets default fault-tolerant mode. Bad structure file option is ignored.
`-s|-spec|-specfile` *specfile*	Use nonstandard patterns spec file.
`-rw|-retitle_with` *prefix*	Add ion state number onto structure titles.

For a more detailed usage summary, use the command

```
$SCHRODINGER/utilities/ionizer -doc
```

For complete documentation on the `ionizer`, see the `README` file:

`$SCHRODINGER/services-v`*version*`/doc/README.ionizer`

Receptor Grid Generation

Glide searches for favorable interactions between one or more typically small ligand molecules and a typically larger receptor molecule, usually a protein. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. The options in each tab of the panel allow you to define the receptor structure by excluding any cocrystallized ligand that may be present, determine the position and size of the active site as it will be represented by receptor grids, and set up Glide constraints. Ligand docking jobs cannot be performed until the receptor grids have been generated.

Receptor grid generation requires a “prepared” structure: an all atom structure with appropriate bond orders and formal charges. In most cases, after ensuring that nonstandard residues have correct bond orders and formal charges, the remainder of the preparation process can be performed automatically using the Protein Preparation panel.

This chapter contains the following information:

- Instructions for using the Receptor Grid Generation panel in preparation for Glide ligand docking, including the setup of hydrophobic constraints.
- A detailed description of the Receptor Grid Generation panel and each of its tabs.

For a brief scientific introduction to Glide, see Chapter 3. For a description of setting up ligand docking jobs, see Chapter 7. For a grid generation tutorial example, see Chapter 4 of the *Glide Quick Start Guide*. Much of the information in this chapter is available in the Maestro online help.

6.1 The Receptor Grid Generation Panel

To open the Receptor Grid Generation panel, choose Receptor Grid Generation from the Glide submenu of the Applications menu. The Receptor Grid Generation panel has three tabs, which you use to specify settings for the receptor grid generation job:

- Receptor
- Site
- Constraints

These tabs are described in later sections of this chapter.

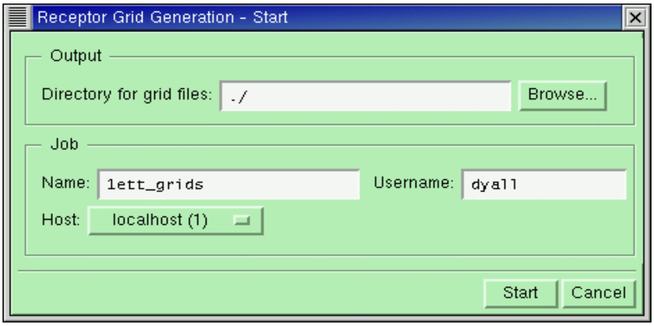


Figure 6.1. The* Start *dialog box for grid generation jobs.

Below the tabs are three buttons:

Start

When you click the Start button, the Receptor Grid Generation - Start dialog box opens. In this dialog box you can specify where you want the output to be saved, by typing the path into the Directory for grid files text box, or browsing for the directory. You can name your job by typing the name into the job Name text box. You can also specify the Username and the Host. To start the job, click Start.

Write

Click Write to write the input files without starting the job.

Reset

Click Reset to restore the default settings in all tabs.

6.2 The Receptor Tab

In this tab you define the part of the Workspace system for which receptor grids should be calculated. You can also scale receptor atom van der Waals radii in this tab. The tab has two sections, Define receptor and Van der Waals radii scaling.

6.2.1 Defining the Receptor

The Define receptor section contains options for defining the part of the system in the Workspace to be treated as the receptor. If only the receptor is included in the Workspace, and no ligand is present, you can ignore the Define receptor options.

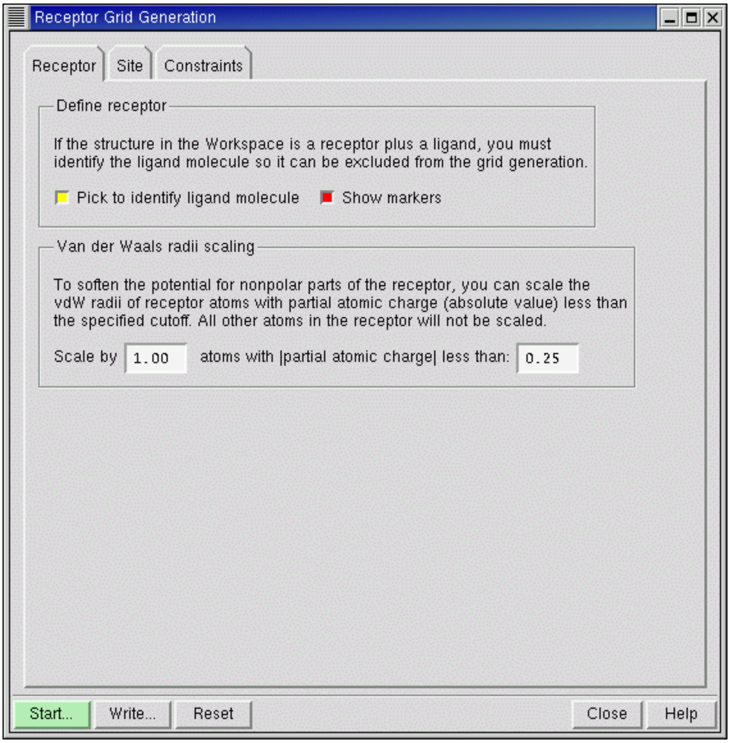


Figure 6.2. The Receptor ***tab of the*** Receptor Grid Generation ***panel.***

If the structure in the Workspace is a receptor with a ligand, use these options to pick the ligand molecule. The ligand will be excluded from receptor grid generation. Everything not defined as the ligand will be treated as part of the receptor. To select the ligand, ensure that Pick to identify ligand molecule is selected, then pick an atom in the ligand molecule. The ligand is now distinguished from the receptor. If Show markers is selected, when the ligand molecule is picked, it is marked with dark green markers. Deselect the option to remove the markers.

6.2.2 Van der Waals Radii Scaling

Glide does not allow for receptor flexibility in docking[1], but scaling of van der Waals radii of nonpolar atoms, which decreases penalties for close contacts, can be used to model a slight "give" in the receptor and the ligand.

You can use the controls in the Van der Waals radii scaling section, described below, to scale the van der Waals radii of those receptor atoms defined as nonpolar by a partial charge

1. This capability is provided by the Induced Fit Docking protocol, which uses Glide and Prime. See the document *Induced Fit Docking* for more information.

threshold you can set. For ordinary Glide docking, it is recommended that receptor radii be left unchanged, and any scaling be carried out on ligand atoms.

The Scale by text box specifies the scaling factor. Van der Waals radii of nonpolar receptor atoms are multiplied by this value. The default value is 1.00, for which no scaling is done.

Scaling of vdW radii is performed only on nonpolar atoms, defined as those for which the absolute value of the partial atomic charge is less than or equal to the number in the text box. Since this is an absolute value, the number entered must be positive. The default for *y* is 0.25.

6.3 The Site Tab

The settings in the Site tab determine where the scoring grids are positioned and how they are prepared from the structure in the Workspace. To make these settings, you need to understand how Glide sets up grids.

Glide uses two "boxes" to organize the calculation:

- The grids themselves are calculated within the space defined by the *enclosing box*. This is also the box within which all the ligand atoms must be contained.
- Acceptable positions for the ligand center must lie within the *bounding box*. This box gives a truer measure of the effective size of the search space.

The only requirement on the enclosing box is that it be big enough to contain all ligand atoms when the ligand center is placed at an edge or vertex of the bounding box. Enclosing boxes that are larger than this are not useful: they take up more space on disk and in memory for the scoring grids, which take longer to compute. The maximum size of the enclosing box is 50 Å.

The ligand center is defined in a rigid-docking run as the midpoint of the line drawn between the two most widely separated atoms. The definition changes slightly for flexible docking, where the ligand center becomes the midpoint between the two most widely separated atoms of the *core region*—the part of the ligand remaining after each of the end-groups has been stripped off at the terminal end of the connecting rotatable bond.

The two boxes share a common center. Thus, the operations in the tab that center one box also center the other.

Each rigidly docked ligand or flexibly docked conformation has an associated length, L, which can be defined as twice the distance from the ligand center to its farthest atom. The required relationship between L and the lengths E and B of the enclosing and bounding boxes for successful placement of the ligand center anywhere within the bounding box is:

$$E \geq B + L$$

The enclosing box must be large enough in each dimension to hold the length of the bounding box plus the maximum length of any ligand. If a larger ligand is encountered, not all positions for the center of the ligand in the bounding box are accessible. The effective bounding box for that ligand will be smaller than the dimension nominally specified. In any docking job using these receptor grids, ligands are confined to the enclosing box.

If the structure in the Workspace consists of a receptor and the ligand molecule you identified in the Receptor tab, Glide uses the position and size of the ligand to calculate a default center and a default size for the enclosing box. When you open the Site tab, the Workspace displays the center of the enclosing box as a set of coordinate axes colored bright green, and the boundaries of the region as a purple wire-frame cube.

If the Workspace structure consists of a receptor only, there is no default center for the enclosing box. The box will not be displayed until you have specified a grid center by selecting residues.

By default, the purple enclosing box outline and the green axes at the center are displayed when you enter the tab. Deselect Display Box to undisplay the box and its center.

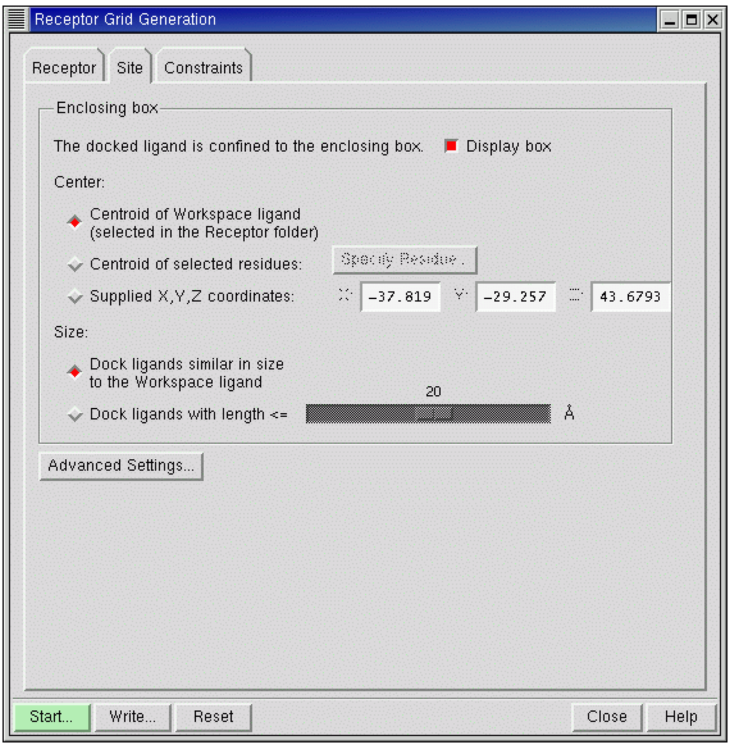


Figure 6.3. The Site ***tab of the*** Receptor Grid Generation ***panel.***

6.3.1 Selecting a Box Center

Select one of the options under Center to determine how the center of the grid is defined:

- Centroid of Workspace ligand

  This option centers grids at the centroid of the ligand molecule that was defined in the Receptor tab, also called the Workspace ligand. If a Workspace ligand has been defined, this option is the default. The Advanced Settings button is available with this option.

- Centroid of selected residues

  This option centers grids at the centroid of a set of residues that you select. With this option you can define the active site (where grids should be centered) with only the receptor in the Workspace. The Specify Residue button is only available when you choose this option; the Advanced Settings button is not available with this option.

  To select the residues, click Specify Residue. The Active Site Residues dialog box opens. Using the picking controls, you can pick the residues that best define the active site. Picked residues are marked in pink when the Active Site Residues dialog box is open. The center and the default boundaries of the enclosing box are calculated and displayed after each residue pick. The list of selected residues is displayed at the top of the dialog box. You can delete residues by selecting them in the list, and clicking Delete. To delete all residues, click Delete All. For more information on picking controls, see Section 2.6 on page 23.

- Supplied X, Y, Z coordinates

  This option centers the grid at the Cartesian coordinates that you specify in the X, Y, and Z text boxes. These text boxes are only available when you choose this option. The Advanced Settings button is available with this option.

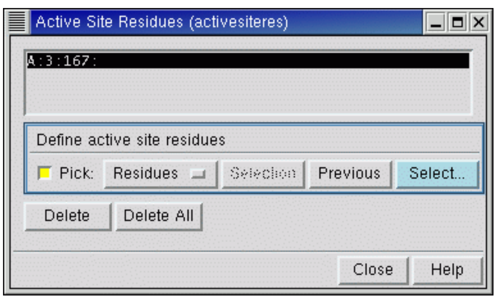


Figure 6.4. The Active Site Residues ***dialog box.***

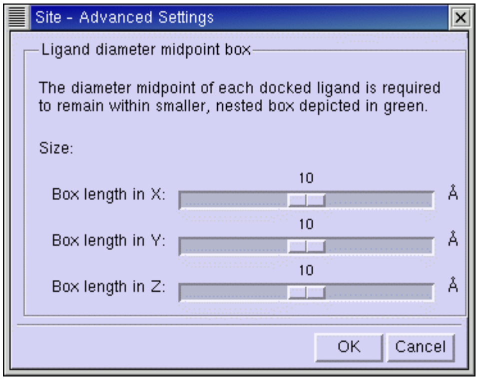


Figure 6.5. The Site - Advanced Settings ***dialog box.***

6.3.2 Setting the Box Sizes

The Size section provides options for the size of the enclosing box. The default option is Dock ligands similar in size to the Workspace ligand, which is suitable when the ligands to be docked are of the same size as, or smaller than, the Workspace ligand. If you expect to dock larger ligands, or if there is no Workspace ligand, select Dock ligands with length <= and use the slider to choose an appropriate maximum ligand length. The slider is set to 20 Å by default.

To change the size of the bounding box, click Advanced Settings. The Site - Advanced Settings dialog box opens, and the bounding box, or *ligand diameter midpoint box,* is displayed as a cube outlined in bright green. The diameter midpoint of each docked ligand must remain within this box. You can use the Size sliders to increase or decrease the dimensions of each side of the box. The default is 10 Å on each side; the allowed range is 6 Å to 14 Å.

A larger ligand diameter midpoint box can be useful to allow ligands to find unusual or asymmetric binding modes in the active site. Conversely, if the default ligand diameter midpoint box allows ligands to stray into regions you know to be unfruitful, you can confine their midpoints to a smaller box, eliminating some of the less useful poses and saving calculation time. Changing the shape of the box can be useful when the active site is spatially extended in one or more directions.

6.4 The Constraints Tab

The Constraints tab of the Receptor Grid Generation panel is used to define Glide constraints for the receptor grids to be generated. Glide constraints are receptor-ligand interactions that you believe to be important to the binding mode, based on structural or biochemical data.

Setting constraints enables Glide to screen out ligands, conformations, or poses that do not meet these criteria early on in their evaluation for docking suitability.

There are four types of Glide constraints available in Glide 4.0: positional constraints, H-bond constraints, metal constraints, and hydrophobic constraints.

- A positional constraint is a requirement that one or more ligand atoms occupy a spherical volume that is centered at a particular position.
- An H-bond constraint is a requirement that a particular receptor-ligand hydrogen bond be formed.
- A metal constraint is a requirement that a particular metal-ligand interaction is present when the ligand is docked.
- A hydrophobic constraint is a requirement that a user-defined number of hydrophobic heavy atoms in the ligand occupy a hydrophobic region in the active site.

The constraints tab has three subtabs, Positional, H-bond/Metal and Hydrophobic, for setting up the constraints. The number of constraints of each type is reported on the subtab tab, and the total number of constraints is reported at the top of the tab. The maximum number of constraints that you can define for a given grid is ten constraints, distributed among positional, H-bond, metal, and hydrophobic constraints.

When constraints setup is complete and the grid generation job is run, Glide writes a file containing the information about the constraints. Subsequent docking jobs use this file to determine whether a given ligand pose satisfies the constraints. If the base name for writing grid files is *gridbase*, the constraints file is named *gridbase*`.cons`. Not all of these constraints are used in a given docking job: when you set up the docking job, you can select up to four constraints to apply to ligand docking.

To use Glide constraints, you must perform both of these steps:

1. Define Glide constraints during grid generation setup.
2. Apply Glide constraints during docking setup.

Any Glide constraints that you want to apply in docking must be defined when the receptor grids are generated.

When you are setting up constraints, it may be helpful to undisplay most of the receptor, leaving only residues within a short distance of the ligand visible.

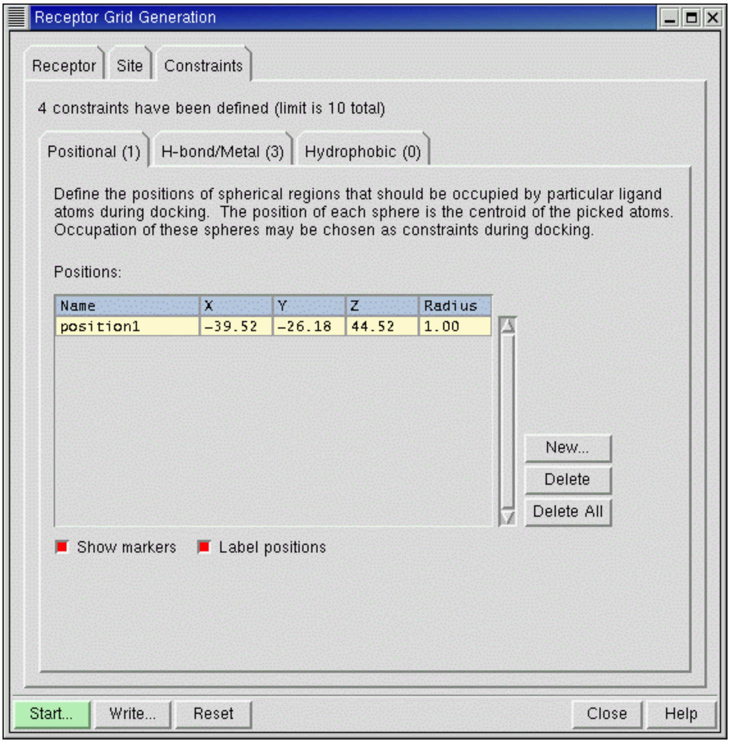


Figure 6.6. The Constraints ***tab of the*** Receptor Grid Generation ***panel showing the*** Positional ***subtab.***

6.4.1 Setting Positional Constraints

Positional constraints define a region that must contain a particular kind of ligand atom. The specific kind of atom is defined during docking setup, using SMARTS patterns. Positional constraints allow you to require interactions between any kind of receptor and ligand atoms, while at the same time placing tighter restrictions on the ligand atom position than is typical with other constraint types.

For example, a hydrogen-bond acceptor in the receptor might be capable of forming hydrogen bonds in two directions, but only one of these results in good binding. While setting an H-bond constraint in this case allows a ligand hydrogen atom to lie in either of these directions, a positional constraint can require it to be in the “good” direction. The constraint could be set by selecting a hydrogen atom that bonds in the “good” direction to define the position of the constraint. For reasons such as this, we suggest that you display a model ligand in the Workspace to aid in selecting appropriate positions for constraints.

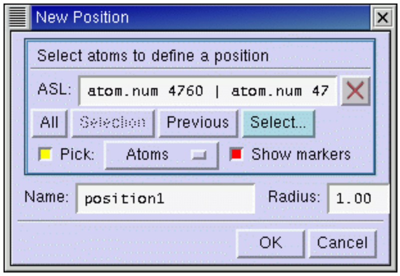


Figure 6.7. The New Position ***dialog box.***

To add a positional constraint, click New. This button opens the New Position dialog box, in which you can pick atoms with the standard picking controls to define a position, name the positional constraint, and specify its radius. The position is the centroid of the selected atoms, and must be inside the enclosing box. While picking is in progress, the constraint is marked with a gray sphere. When you click OK, the constraint is added to the Positions table if it is inside the enclosing box; otherwise a warning is displayed.

To delete a constraint, select it in the Positions table and click Delete; to delete all constraints, click Delete all.

The Positions table displays the positional constraints you have chosen, giving the name, coordinates, and radius of the constraint sphere for each constraint. The coordinates and the radius are given in angstroms. You can select a single constraint in the table, and edit the name, coordinates, and radius of the sphere by clicking in the table cell and changing the value.

To view the positional constraints in the Workspace, select Show markers. The selected constraint is marked by a yellow sphere. The other positional constraints are marked by red spheres. If Show markers is selected, selecting the Label positions option displays the name of the constraint in the Workspace. The labels are colored the same as the constraints.

6.4.2 Setting H-Bond and Metal Constraints

Up to ten symmetry-distinct receptor atoms can be chosen as possible H-bond or metal constraint sites.

For hydrogen-bonding interactions, the receptor atom must be a polar hydrogen (including thiol H in cysteine), nitrogen, or oxygen. If you choose an atom with one or more symmetry-equivalent atoms in its functional group, the symmetry-equivalent atoms will all be selected as well, and collectively count as one constraint. For example, if you create a constraint by picking one oxygen atom of a carboxylate group, Glide includes the other oxygen atom in the same constraint. A ligand interaction with either oxygen atom will satisfy that single constraint.

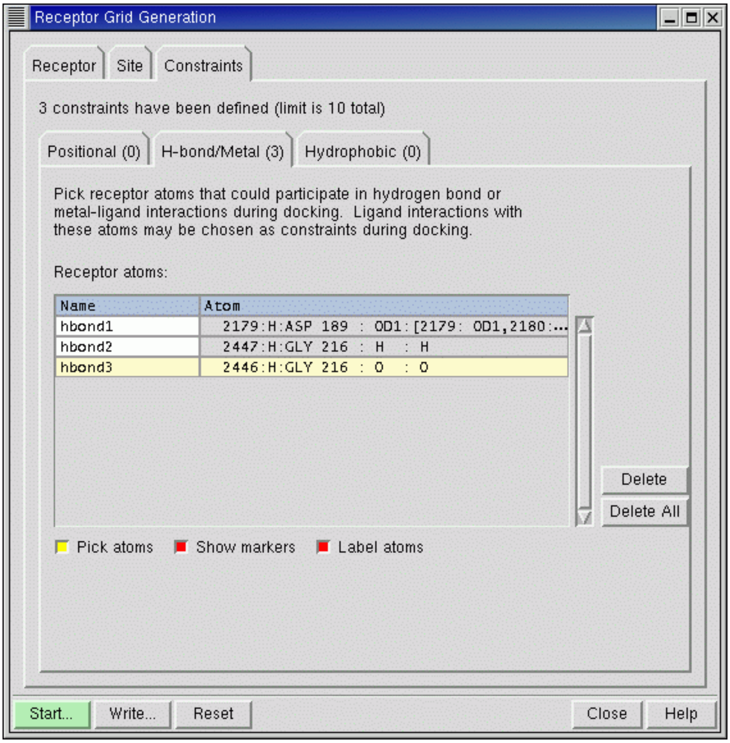


Figure 6.8. The Constraints ***tab of the*** Receptor Grid Generation ***panel showing the*** H-bond/Metal ***subtab.***

For metal-ligand interaction constraints, the receptor atom must be a metal ion. Metal-ligand constraints can also include restrictions on the formal charges of the interacting ligand atoms. These requirements are added during the setup of docking jobs.

The receptor atoms selected must also be close enough to the ligand that satisfying the constraints is possible. You do not need to specify limits on distances or angles between receptor and ligand atoms for the constraint: Glide sets these values internally, to H-acceptor distances of 1.2 to 2.5 Å; donor angles greater than 90°, and acceptor angles greater than 60°. These values are looser than those employed by Maestro. General distance requirements are incorporated using the enclosing box for the ligand. The receptor atoms selected for constraints must be inside the enclosing box (which is displayed in purple) or within bonding range of it.

To display hydrogen bonds in the Workspace, choose Inter from the Display H-bonds button menu and click on a ligand atom. The hydrogen bonds between the ligand and the receptor are displayed. This should make it easier to locate the relevant receptor atoms. If you want to use the looser criteria for hydrogen bonds employed by Glide, select Measurements from the Tools menu and change the values in the H-bonds tab.

To set H-bond or metal constraints, ensure that Pick atoms is selected in the H-bond/Metal constraints tab, and pick the desired atoms in the Workspace. Glide automatically includes symmetry-equivalent atoms such as the other oxygen in a carboxylate group. If Show markers is selected, a red cross and red padlock appear next to each atom picked. If the picked atom is one of a set of symmetry-equivalent atoms, all the atoms in the set are marked. If Show markers is selected, selecting Label atoms displays the constraint name in the Workspace.

As you select atoms in the receptor, they appear in the Receptor atoms list in the format

atom-number:*chain*:*residue-name residue-number* :*atom-name* : *symmetry-set*

where

- *atom-number* is the Maestro atom number
- *chain* is the chain name
- *residue-name* is the name of the residue
- *residue-number* is the residue number and the insertion code, if any
- *atom-name* is the PDB atom name
- *symmetry-set* is the atom name or symmetry-equivalent atom set

for example,

341:C:ASN 239 : OD1 : ODn

If the picked atom is part of a symmetry equivalent set, its identification is followed by square brackets enclosing the number and name of each atom in the set, separated by commas.

To delete a single H-bond or metal constraint, select it in the list and click Delete; to delete all the listed constraints, click Delete All.

6.4.3 Setting Hydrophobic Constraints

A hydrophobic constraint requires that a hydrophobic region of the receptor be occupied by one or more hydrophobic heavy atoms in the ligand. The possible hydrophobic regions are identified from a hydrophobic map of the receptor site. You can select one or more of the hydrophobic regions as a constraint, and determine the size of the region that must be occupied by adding or deleting cubic volumes (“cells”) to the region. When you set up a docking job, you can select one or more of these regions and specify how many atoms must occupy each region. The tools for generating the hydrophobic map and defining the hydrophobic constraint regions are in the Hydrophobic subtab of the Constraints tab.

6.4.3.1 Generating the Hydrophobic Map

To set up a hydrophobic constraint, you must first run a job to generate the hydrophobic map of the receptor site. To generate the hydrophobic map, click Locate Hydrophobic Cells in the

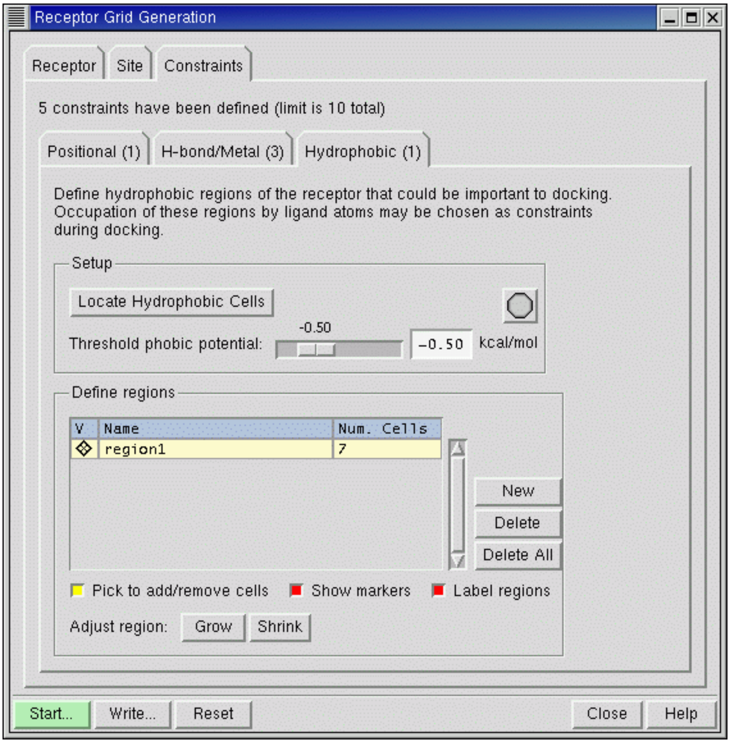


Figure 6.9. The* Constraints *tab of the* Receptor Grid Generation *panel showing the* Hydrophobic *subtab.

Setup section. A SiteMap job is started, which takes a few minutes. The gray octagon at the upper right of the panel turns green and spins; when the job finishes it turns gray again.

Translucent gray cubes that represent the hydrophobic regions around the active site should be displayed when the job finishes. If they are not, adjust the Threshold phobic potential slider until they appear. A less negative threshold enlarges the hydrophobic region; a more negative threshold diminishes the hydrophobic region. The threshold corresponds to the isovalue contour at which the hydrophobic map is displayed, and has a default value of –0.5.

6.4.3.2 Defining Hydrophobic Constraint Regions

After the hydrophobic map has been generated, the table in the Define regions section contains a single default constraint region, `region1`, with 0 in the Num. Cells column (equivalent to no constraint). You can change the name of a region in the Name column, or turn off the visualization markers for a region by deselecting the box in the V column.

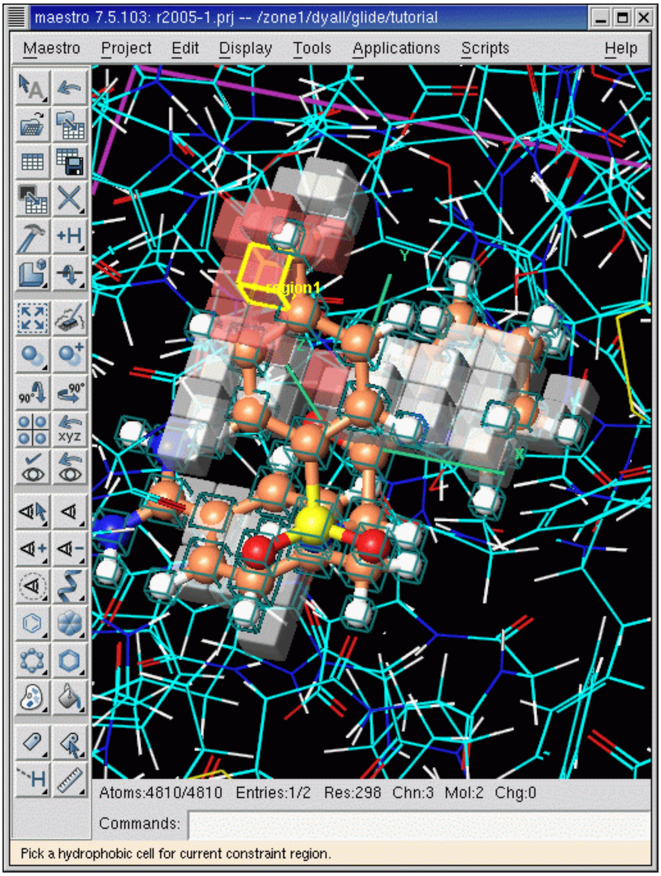


Figure 6.10. Hydrophobic constraint regions displayed in the Workspace.

A region is defined by a set of hydrophobic cells. The cells in the region do not have to be contiguous. To add individual cells to a region, you can select Pick to add/remove cells and click on cells in the Workspace. When you select this option, the cursor has the label C, to indicate that cell picking is active. The cell color changes to red when it is added. The last picked cell is outlined in yellow. To delete a cell that has already been added, click on the cell in the Workspace. Its color changes to gray. (See Figure 6.10.)

You can also add cells and remove cells using the Grow and Shrink buttons. When you click Grow, the cells that are nearest neighbors to the cell outlined in yellow are added to the defined region (colored red). Clicking Grow a second time selects a layer of cells adjacent to those most recently selected. This process can be repeated until the entire block of cells is selected. To remove layers of cells added using Grow, click Shrink. Each click removes one layer.

To add a new hydrophobic constraint region, click New. A row is added to the table with a default name of `region`*n*. To delete a constraint region, click Delete.

When the Label regions option is selected (the default), regions are labeled in the Workspace with their Name from the Define regions table.

Ligand Docking

Glide ligand docking jobs require a set of previously calculated receptor grids and one or more ligand structures. Information on setting up grid generation jobs is given in Chapter 6. For a docking tutorial example, see Chapter 5 of the *Glide Quick Start Guide*.

For accurate docking, the ligands you specify must satisfy these four conditions:

1. Ligands must be three-dimensional (3D) structures.
2. Ligands must each consist of a single molecule with no covalent bonds to a receptor and no accompanying fragments such as counter ions.
3. Ligand files must be in SD, PDB, or Maestro format. Ligand files in MacroModel format can be converted by importing them into Maestro and exporting them in Maestro format.
4. Ligands must have all their hydrogens (filled valences). These can be added in Maestro.

Preparation of the ligands before docking is strongly recommended. LigPrep or MacroModel can be used to prepare ligands—see Chapter 5 for more information.

If a correct Lewis structure cannot be generated for a ligand, it will be skipped by the docking job. Glide also automatically skips ligands containing unparametrized elements, such as arsenic, or atom types not supported by the OPLS force fields, such as explicit lone pair "atoms."

This chapter contains the following information:

- A detailed description of the Ligand Docking panel in Maestro and each of its tabs, including instructions for applying Glide constraints, using similarity, using extra-precision Glide docking (Glide XP), and distributed processing.
- A description of the Glide Pose Viewer panel.

7.1 The Ligand Docking Panel

To open the Ligand Docking panel, choose Ligand Docking from the Glide submenu of the Applications menu. The Ligand Docking panel has five tabs:

- Settings
- Ligands
- Constraints
- Similarity
- Output

These tabs are described in the following sections of this chapter. You use the options in these tabs to specify settings for the ligand docking job. When you have completed your setup, the following buttons allow you to process your job:

- Start—Open the Ligand Docking - Start dialog box to start the job
- Write—Write the input files to disk without starting the job
- Reset—Discard settings and restore the default settings in all tabs

The Ligand Docking - Start dialog box provides controls for the running of the job. You can name the job in the Name text box, and specify the host and the user name on the specified host. You can also specify options for distributed processing. By default, the job is run serially. To separate the docking job into subjobs that are run in parallel, enter the number of subjobs in the Separate docking into *n* subjobs text box, then select one of the following options to set the number of processors to use:

- Distribute subjobs over maximum available processors
- Distribute subjobs over *p* processors

If Glide is installed on the LSF Desktop or GridMP grid servers, you can select one of these servers to run the job. When you have finished making settings, click Start to start the job.

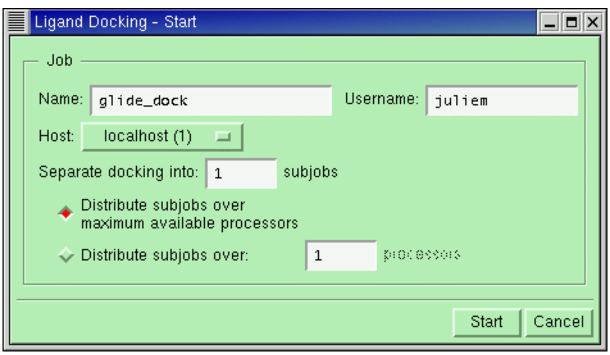


Figure 7.1. The Start ***dialog box for ligand docking jobs.***

7.2 The Settings Tab

The Settings tab defines the basic options for docking ligands: specifying the grid, selecting the precision, and setting flexibility options. You can also make settings for the selection of initial poses and for the energy minimization of the poses that pass the initial selection in the Settings - Advanced Settings dialog box. To open this dialog box, click Advanced Settings. The settings, both basic and advanced, are described in the following subsections.

7.2.1 Specifying the Receptor Grid

To specify the receptor grid for the docking job, click Browse in the Receptor grid section of the Settings tab to open a file selector and choose a grid file (`.grd`). The file name, without the `.grd` extension, is displayed in the Receptor grid base name text box. You can also enter the base name directly into the text box.

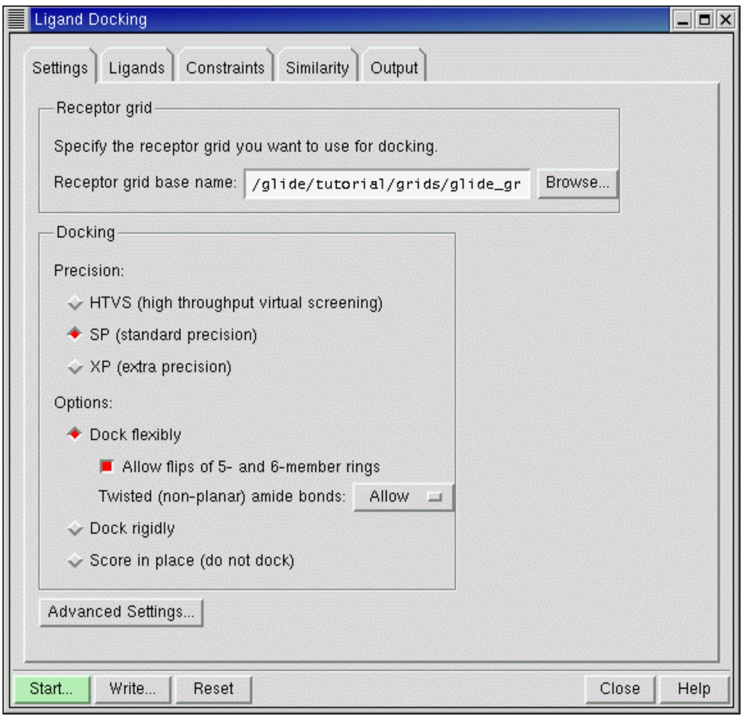


Figure 7.2. The** Settings **tab of the** Glide **panel.

7.2.2 Selecting the Docking Precision

There are three choices of docking precision, given under Precision in the Docking section.

- HTVS (high-throughput virtual screening)—High-throughput virtual screening (HTVS) docking is intended for the rapid screening of very large numbers of ligands. HTVS has much more restricted conformational sampling than SP docking, and cannot be used with constraints, score-in-place, or rigid docking. Advanced settings are not available for HTVS, but are fixed at predetermined values.
- SP (standard precision)—Standard-precision (SP) docking is appropriate for screening ligands of unknown quality in large numbers. Standard precision is the default.
- XP (extra precision). Extra-precision (XP) docking and scoring is a more powerful and discriminating procedure, which takes longer to run than SP. XP is designed to be used on ligand poses that have a high score using SP docking. We recommend that you run your database through SP docking first, then take the top 10% to 30% of your final poses and dock them using XP, so that you perform the more expensive docking simulation on worthwhile poses. For more information on XP docking, see Section 3.4 on page 36.

  Note: Extra precision is not available for active sites containing metals.

7.2.3 Setting Docking Options

Under Options in the Docking section of the Settings tab, you can choose whether ligands are docked flexibly, rigidly, or not at all (score in place), and set options for conformation generation. These options are described below.

Dock flexibly

This is the default option, and directs Glide to generate conformations internally during the docking process; this procedure is known as *flexible docking*. At present, conformation generation is limited to variation around acyclic torsion bonds, generation of conformations of nonaromatic five- and six-membered rings, and generation of pyramidalizations at certain trigonal nitrogen centers, such as in sulfonamides. You can control whether ring conformations are generated or not with the option Allow flips of 5- and 6-member rings. This option is selected by default.

For amide bonds, you can control the behavior with the Twisted (non-planar) amide bond option menu. In SP and HTVS docking modes, this menu has two options: Allow and Forbid. Selecting Forbid freezes amide bonds in their input conformation throughout docking. The default is Allow. In XP docking mode, this menu has the options Penalize and Do not penalize. Selecting Penalize applies penalties to amide bonds that are not cis or trans, rather than freezing them entirely. The default is Penalize.

Dock rigidly

"Rigid" docking allows the existing ligand structure to be adjusted, but skips the conformation generation step.

Score in place (do not dock)

When this option is selected, Glide does no docking, but rather uses the input ligand coordinates to position the ligands for scoring. This option is useful to score the native ligand in its cocrystallized or modeled position, or as a post-processing step on Glide-generated poses to obtain individual components of the GlideScore prediction of the binding affinity.

Note: You cannot score in place the ligand that is defined as the reference ligand for calculation of the RMSD in conformational comparisons.

7.2.4 Selection of Initial Poses

The options in the Selection of initial poses section of the Settings - Advanced Settings dialog box control the way poses pass through the filters for the initial geometric and complementarity "fit" between the ligand and receptor molecules. The grids for this stage contain values of a *scoring function* representing how favorable or unfavorable it would be to place ligand atoms of given general types in given elementary cubes of the grid. These cubes have a constant spacing of 1 Å. The "rough score" for a given *pose* (position and orientation) of the ligand relative to the receptor is simply the sum of the appropriate grid scores for each of its atoms. By analogy with energy, favorable scores are negative, and the lower (more negative) the better.

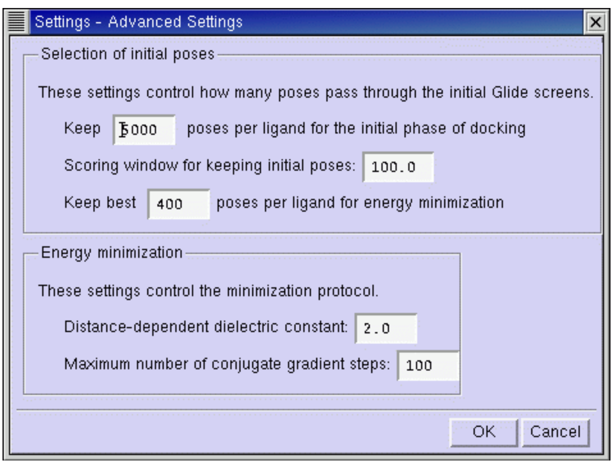


Figure 7.3. The Settings - Advanced Settings ***dialog box.***

The initial "rough scoring" is done on a coarse grid, on which the possible positions for placing the ligand center are separated by 2 Å, twice the elementary cube spacing, in *x*, *y*, and *z*. The "refinement" step rescores the successful rough-score poses after the particular rigid translational repositioning of –1.0 Å or +1.0 Å in *x*, *y*, and *z* that gives the best possible score. This procedure effectively doubles the resolution of the scoring screen.

Poses that pass these initial screens enter the final stage of the algorithm, which involves evaluation and minimization of a grid approximation to the OPLS-AA nonbonded ligand-receptor interaction energy.

This section contains three text boxes in which you can set parameters for the initial screening:

Keep *n* initial poses per ligand for the initial phase of docking

This text box sets the maximum number of poses per ligand to pass to the grid refinement calculation. The value must be a positive integer. The default setting depends on the type of docking specified and whether Glide constraints have been applied:

- 5000 poses for flexible docking jobs in general
- 500 poses for flexible docking jobs to which Glide constraints are applied
- 1000 poses for rigid docking jobs (Glide constraints do not change this value)

Scoring window for keeping initial poses

This text box sets the rough-score cutoff for keeping initial poses, relative to the best rough score found so far. The value must be positive. The default window is 100.0 kcal/mol, meaning that to survive, a pose must score within 100.0 kcal/mol of the best pose. Using the default window, for example, if the best pose found so far has a score of -60.0 kcal/mol, poses with a score more positive than 40.0 kcal/mol will be rejected.

Keep best *m* poses per ligand for energy minimization

This text box specifies the number of poses per ligand to be energy minimized on the OPLS-AA nonbonded-interaction grid. The default setting depends on the type of docking specified.

- 400 poses for flexible docking jobs in general.

  For extra-precision (XP) docking, the minimum number of poses is internally adjusted to 800 instead of 400, assuming at least 800 poses per ligand have been kept.

- 40 poses for flexible docking jobs to which Glide constraints are applied.

- 100 poses for rigid docking jobs (Glide Constraints do not change this value).

The range for this value is 1 to *n*, where *n* is the value in the Keep *n* initial poses per ligand for the initial phase of docking text box.

7.2.5 Energy Minimization Settings

The energy minimization stage of the docking algorithm minimizes the energy of poses that are passed through the Selection of initial poses scoring phase. The Energy minimization section of the Settings - Advanced Settings dialog box contains two options:

Distance-dependent dielectric constant

Glide uses a distance-dependent dielectric model in which the effective dielectric "constant" is the supplied constant multiplied by the distance between the interacting pair of atoms. The default setting is 2.0, and Glide's sampling algorithms are optimized for this value. Although this text box allows you to set the dielectric constant to any real value greater than or equal to 1.0, changing this setting is not recommended.

Maximum number of conjugate gradient steps

This text box specifies the maximum number of steps taken by the conjugate gradient minimization algorithm. The value must be greater than or equal to 0; the default value is 100. Setting the value to 0 results in a single-point energy calculation on each pose that survives rough-score screening, or on the single initial pose if no screening was done.

7.3 The Ligands Tab

In the Ligands tab you specify the source of ligands to be docked or scored and set size limits for skipping ligands. You can also change the settings for van der Waals radii scaling of nonpolar ligand atoms. If you want to define a reference ligand structure for use in rms comparisons of docking accuracy, you can use the options in the Advanced Settings dialog box, which is opened by clicking the Advanced Settings button in the lower part of the panel.

7.3.1 Specifying the Source of the Ligands

In the Ligands to be docked section you specify the source of ligands to be docked (or scored in place). To specify the source, choose one of the following options under Use ligands from:

File

If you select File as the source of ligands, you can type the file name in the File name text box, or click the Browse button to open a file selector, in which you can choose the format and navigate to the ligand file. The file must be in Maestro, SD, or PDB format.

By default, all structures in the file are docked. To select a contiguous subset of ligands from the file, enter values in the Range text boxes. To enter the upper limit, you must deselect End. The End option allows you to dock all ligands from a particular ligand to the end of file.

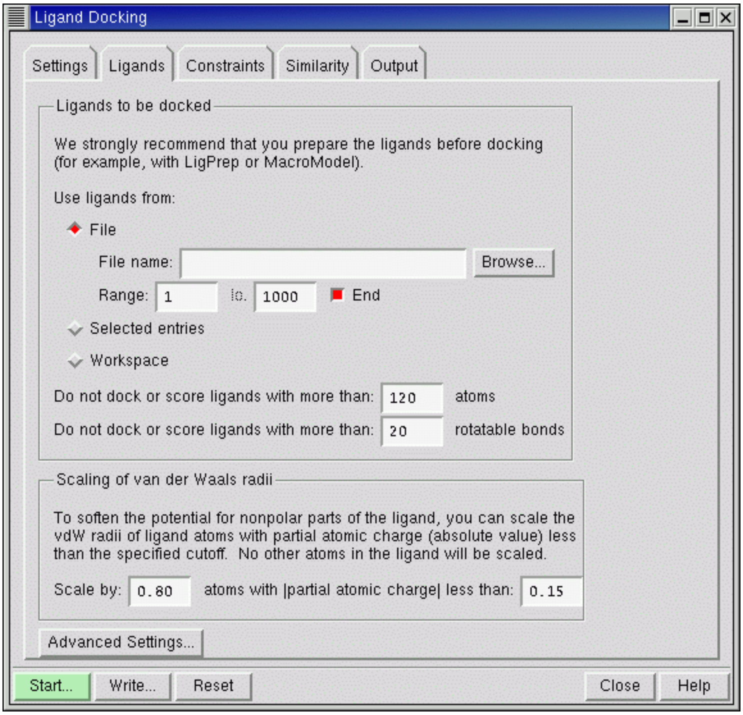


Figure 7.4. The Ligands ***tab of the*** Ligand Docking ***panel.***

The ability to select a subset of ligands is useful if a problem with Glide or with the input ligand causes a submitted Glide job to terminate abnormally. Then you can set the initial ligand number when you restart the job to pick up after the point in the input ligand file at which the problem occurred.

Selected entries

Select this option to dock ligands that are selected entries in the Project table.

Workspace

Select this option to dock the structure in the Workspace. If you select this option, only a single entry is permitted in the Workspace, and this entry is treated as the ligand to be docked. You should therefore ensure that the structure in the Workspace is the ligand to be docked, without the receptor or any other structures.

7.3.2 Setting Restrictions on the Ligands To Be Docked

In the text boxes at the end of the Ligands to be docked section, you can set limits on structural feature counts to screen out structures before docking. These text boxes are described below.

Do not dock or score ligands with more than *a* atoms

This text box sets the maximum number of atoms a ligand structure may have if it is to be docked. Ligand structures in the input file that have more than the specified number of atoms will be skipped. The default is 120 atoms. You can reduce the maximum number of atoms *a*, if the active-site region is small and enclosed, to speed up a docking calculation on a large ligand database. The maximum number of atoms that you can set is 200.

Do not dock or score ligands with more than *r* rotatable bonds

This text box sets the maximum number of rotatable bonds a ligand structure may have if it is to be docked. Ligand structures in the input file that have more than this number of rotatable bonds will be skipped. The default is 20 rotatable bonds. If only relatively small or rigid ligand "hits" are wanted, you can decrease the value of *r*. Alternatively, you can increase *r* up to a maximum allowable value of 35 rotatable bonds.

7.3.3 Van der Waals Radii Scaling

Glide does not allow for flexible receptor docking.[2] However, successful docking sometimes requires that the ligand and the receptor "give" a bit in order to bind. To model this behavior, Glide can scale the van der Waals radii of nonpolar atoms (where nonpolar is defined by a partial charge threshold you can set), thereby decreasing penalties for close contacts. Scaling is performed for qualifying atoms in the ligand, but not those in the receptor. Ligand atom radii scaling settings can be changed using the options in this section. To scale receptor atom radii, you must choose the appropriate options in the Receptor tab of the Receptor Grid Generation panel prior to grid generation.

Scale by *x* atoms with |partial atomic charge| less than *y*

The Scale by *x* text box specifies the scaling factor. The default is 0.80. To turn van der Waals radii scaling off, set the scaling factor to 1.0. Full penalties for close contacts of nonpolar ligand atoms will then be used.

Scaling is performed only on nonpolar atoms, defined as those for which the absolute value of the partial atomic charge is less than or equal to the number in the text box. Since this is an absolute value, the number entered must be positive. The default for ligand atoms is 0.15.

2. Flexible receptor docking can be performed with the Induced Fit Docking solution, which uses Glide with Prime to allow for receptor flexibility. For more information, see the document *Induced Fit Docking*.

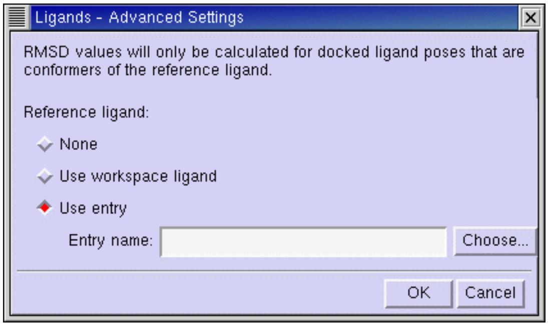


Figure 7.5. The* Ligands - Advanced Settings *dialog box.

7.3.4 Specifying a Reference Ligand for RMSD Calculations

In the Ligands - Advanced Settings dialog box, you can specify a *reference ligand* for Glide to use in rms comparisons with conformationally-related ligands in the docking job. When a ligand being docked is recognized as a conformer of the reference ligand, Glide reports the rms distance between non-hydrogen atoms of the docked ligand and the reference ligand. To be recognized as conformers, they must be topologically equivalent, and the ordering of corresponding atoms must be the same.

To open this dialog box, click Advanced Settings. The options for specifying a reference ligand are:

- None

  Do not use a reference ligand. This option is selected by default.

- Use Workspace ligand

  Use the ligand currently included in the Workspace as the reference ligand. To use this option, the structure in the Workspace must be the ligand alone, without the receptor.

- Use entry

  To select an entry in the project table as the reference ligand, select this option, and then either type the entry name directly into the adjacent text box, or click Choose to display a list of all the entries in the current project, from which one entry can be selected.

7.4 The Constraints Tab

The Constraints tab lists all the Glide constraints that are defined for the receptor grid file you specified in the Settings tab, and provides the means to apply these constraints in docking. The available constraints are shown in the Workspace if Show markers is selected and the receptor is displayed. To display the receptor, click Display Receptor. Positional constraints are marked with gray spheres. Atoms for which H-bond/metal constraints are defined are marked with a red asterisk and padlock. Regions for which hydrophobic constraints are defined are marked with translucent gray hydrophobic cells.

Constraints are applied during docking by identifying the relevant features in the ligand, and requiring specified atoms in those features to be spatially confined to the constraint region. The ligand features and the atoms in those features that must be constrained are defined in terms of SMARTS patterns. You can customize the features in the Edit Feature dialog box, which is described in Section 7.4.2 on page 92. For positional constraints, no default features are defined, so you must provide a feature definition in the Edit Feature dialog box.

Glide constraints cannot be used in HTVS mode.

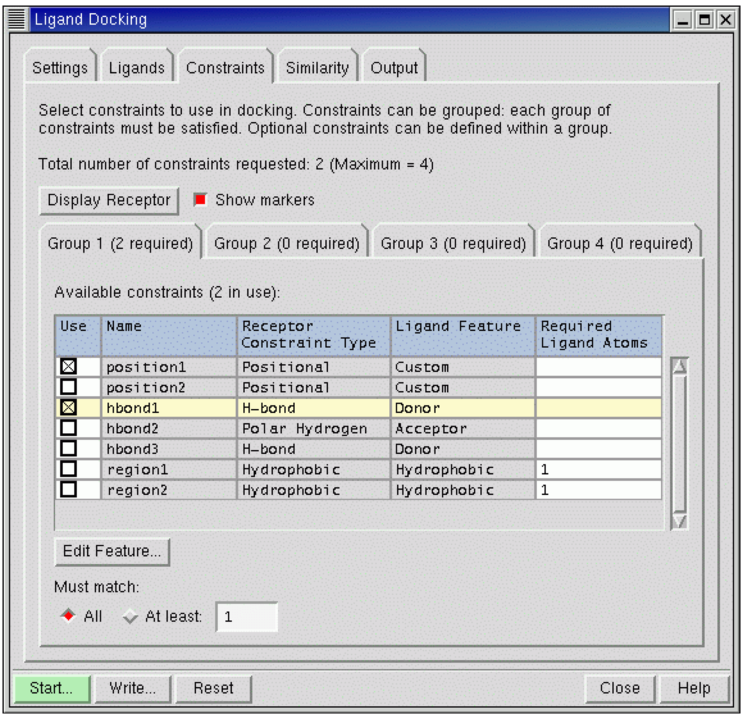


Figure 7.6. The* Constraints *tab of the* Ligand Docking *panel.

Only the constraints you select will be applied in the ligand docking job you are setting up. If there are no constraints selected when you start the docking job, no constraints will be applied.

7.4.1 Setting Constraints

To allow some flexibility in setting constraints, including optional constraints, Glide provides four constraint groups, presented in subtabs labeled Group 1 through Group 4. If you want to set simple constraints you can do so in the Group 1 tab, which is displayed by default, and ignore the remaining groups.

Each subtab contains a table of all the available constraints (described in Table 7.1), an Edit Feature button, and two Must match options. To set constraints within a tab, first click the Use column for each of the desired constraints. An X appears in the check box. If the receptor is displayed and Show markers is selected, the hydrophobic and positional constraint markers turn red when the constraint is selected, and the H-bond and metal constraint markers turn turquoise. The number of constraints you selected is displayed next to the table title. Next, decide whether all the constraints should be applied, or only some of them.

- If you want all of the chosen constraints to be applied, select All under Must match.
- If you want some of the chosen constraints to be applied, select At least under Must match, and enter the number of constraints that must be satisfied in the text box. For example, if you chose three hydrogen-bond acceptors, and you want any two out of the three to be satisfied, you would enter 2 in the text box.

The number of constraints that are required is displayed in the subtab tab, and is added to the total, which is displayed in the upper part of the Constraints tab.

To unset a constraint that you have set, click the Use column again. The X in the check box disappears.

More complex constraints can be applied by using more than one constraint group. If you set constraints in more than one group, each group of constraints is applied to the ligand (that is, a Boolean AND is applied between groups). The general syntax of the constraints is (N1 required from Group 1) AND (N2 required from Group 2) AND (N3 required from Group 3) AND (N4 required from Group 4).

For example, suppose the grid contains a hydrogen bond constraint hbond1 and two hydrophobic constraints hphob1 and hphob2. If you want to enforce the hydrogen bond constraint, and require only one of the two hydrophobic constraints, you would use two groups. In Group 1, you would click the Use check box for hbond1 and select All under Must match. In Group 2, you would click the Use check boxes for hphob1 and hphob2, select At least under Must match, and enter 1 in the text box. Both groups are applied. The resulting constraints can be represented as “hbond1 AND (hphob1 OR hphob2)”.

Table 7.1. Description of the Available constraints *table.*

Column	Description
Use	Check box to select the constraint for use in docking. Click to select or deselect.
Name	Constraint name. This is the name defined in the Constraints tab of the Receptor Grid Generation panel.
Receptor Constraint Type	Type of receptor constraint. Hydrogen bond constraints are classified into H-bond for hydrogen-bond acceptors and Polar Hydrogen for hydrogen-bond donors (i.e. hydrogen atoms).
Ligand Feature	Name of the feature in the ligand that must match the constraint. The available features are: Acceptor, Charged Acceptor, Neutral Acceptor, Donor, Hydrophobic, and Custom. By default, the feature that matches a receptor polar hydrogen is set to Acceptor; for a receptor H-bond type it is Donor, for a receptor hydrophobic feature it is Hydrophobic, and for a positional constraint it is Custom. Custom is undefined by default, so you must edit this feature to define the patterns that match the desired ligand atoms.
Required Ligand Atoms	In this column, the number of ligand atoms that must occupy a hydrophobic region can be set. The value is only meaningful for hydrophobic constraints.

If your desired constraint specification cannot be put in the general form above, you might be able to achieve your goal by running more than one docking job with a separate constraint specification for each. For example, if you want to apply the constraints "(hbond1 AND hphob1) OR (hbond2 AND hphob2) OR (hbond3 AND hphob3)", you could run three separate docking jobs, one with (hbond1 AND hphob1) set, one with (hbond2 AND hphob2) set, and one with (hbond3 AND hphob3) set.

The total number of required constraints, summed over all groups, must be four or fewer. The number in parentheses after the group name in the subtab tab is the number of constraints that must be satisfied in this group. If you selected All, it is the number of constraints you chose. If you selected At least, it is the value in the At least text box.

A default ligand feature definition is supplied and assigned to each receptor constraint type, with the exception of positional constraints, for which the Custom feature is undefined. To change either the assignment or the feature definitions, use the Edit Feature dialog box, as described in the next section. You can select the same constraint in more than one group, but the assignment and the feature definitions are the same for each group.

Note: To use positional constraints, you *must* define the ligand feature that it should match. No default feature definition is provided, and the job cannot be run until a feature definition is provided. To define the ligand feature, select the appropriate row in the Available constraints table and click Edit Feature. The feature can then be defined in the Edit Feature dialog box.

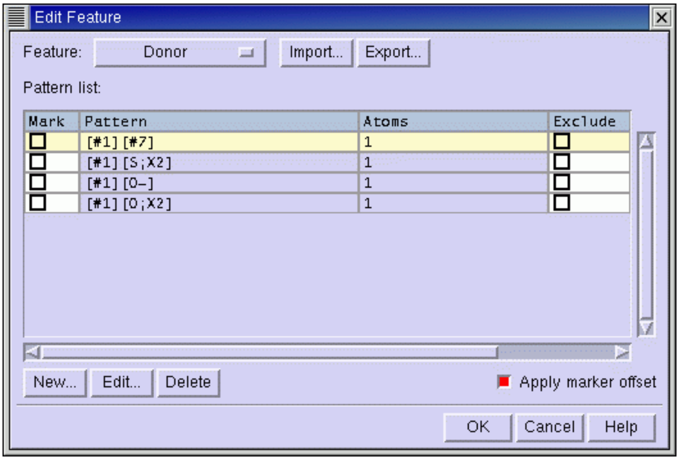


Figure 7.7. The Edit Feature ***dialog box.***

7.4.2 Defining Ligand Features

Ligand features are identified by matching to a collection of SMARTS patterns that defines a feature type. There are six feature types: Acceptor, Charged Acceptor, Neutral Acceptor, Donor, Hydrophobic, and Custom. The feature definitions for these six types form a feature set, which can be imported and exported. Each constraint can have its own feature definition, so you can have a different definition of a given feature type for each constraint. However, the same feature definition from the same set is used for a given constraint in all groups. For each feature definition, you can add patterns, edit and delete custom patterns, and define patterns for exclusion of functional groups. Feature sets can be imported and exported. These tasks are carried out in the Edit Feature dialog box, which you open by clicking Edit Feature.

To change the feature type assigned to the constraint or to edit the feature definition for a particular constraint, select the row in the Available constraints table, and click Edit Feature.

If you only want to change the feature type assigned to the constraint, choose the feature type from the Feature menu, and click OK. The change is reflected in the Ligand Feature column of the Available constraints table, and applies to all groups. If you want to edit the feature definition, follow the instructions in Section 7.4.2.2 and Section 7.4.2.3.

7.4.2.1 Loading and Saving Feature Sets

Built-in feature sets are stored with the distribution, so you do not need to create your own, except for positional constraints.

You can import a feature set for the selected constraint from a file by clicking Import, and navigating to the feature file. When you import a feature set, the definitions of all feature types are replaced, not just the feature type chosen from the Feature menu. The feature definitions are replaced only for the selected constraint, but are replaced for that constraint in all groups.

Feature sets can be saved to a file by clicking Export, and specifying the file location in the file selector that is displayed.

7.4.2.2 Adding, Editing, and Deleting Patterns

The patterns that define a feature are displayed in the Pattern list table (see Table 7.2) when you choose the feature type from the Feature option menu.

Table 7.2. Description of Pattern list *table.*

Column	Description
Mark	Column of check boxes. Selecting a check box marks the pattern on any structures that are displayed in the Workspace.
Pattern	Pattern definition. The definitions are SMARTS strings.
Atoms	The list of atoms that must match the pattern, numbered according to the SMARTS string.
Exclude	Column of check boxes. If a check box is selected, the atoms in other patterns are matched only if they do not match this pattern. This is essentially a NOT operator. Excluded patterns are processed before other patterns.

If the patterns in a given feature definition do not cover all the functional groups that you want to include in the definition, you can add extra patterns. Matching of patterns to ligand structures is done in the order specified in the Pattern list table. You cannot change the order of the patterns once they are in the table, so you must add new patterns at the appropriate point. If you want to move a pattern, you must delete it and add it again.

To add a new SMARTS pattern, click the table row above which you want the pattern to be inserted, then click New. In the New Pattern dialog box (Figure 7.8), you can provide a SMARTS pattern and define the atoms that must satisfy the constraint: the acceptor or donor atoms, for example.

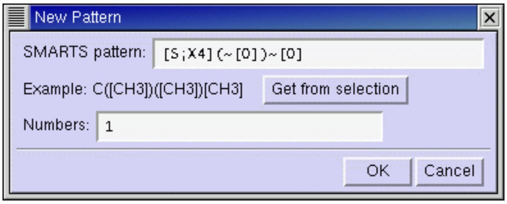


Figure 7.8. The New Pattern ***dialog box.***

There are two ways to provide a SMARTS string. The first is to type the string into the SMARTS pattern text box. The second is to select atoms in the Workspace, then click Get from selection. Maestro generates a SMARTS string for the selected atoms and places it in the SMARTS pattern text box. You can then edit it if you like. You should make sure that you have a suitable molecule, such as a known active ligand, in the Workspace before you open the Edit Feature dialog box. This procedure can be slow if large molecules, such as a receptor, are displayed in the Workspace.

The atoms in the ligand that must satisfy the constraint are specified in terms of the SMARTS pattern. For positional, metal, and H-bond constraints, only one atom should be specified. For hydrophobic constraints, the non-hydrogen atoms of the hydrophobic group should be specified. To specify the atoms, enter the atom numbers as a comma-separated list in the Numbers text box: atom 1 is the first atom in the SMARTS pattern, and so on.

When you click OK, a new row is added to the Pattern list table.

To edit a pattern, select the table row for the pattern, then click Edit. In the Edit Pattern dialog box, you can modify the SMARTS pattern or get a new pattern from the Workspace selection, and change the atoms in the pattern that must satisfy the constraint. The Edit Pattern dialog box is identical to the New Pattern dialog box except for the title.

To delete a pattern, select the table row for the pattern, then click Delete.

7.4.2.3 Excluding Functional Groups from a Feature

If you want to ensure that certain functional groups are not matched, you can select the check box in the Exclude column for the pattern for that group. For example, you might want to exclude a carboxylic acid group from being considered as a hydrogen bond donor, because it will be ionized under physiological conditions. Excluded patterns are processed first, regardless of their position in the Pattern list table. Thus, an excluded pattern prevents the atoms that match it from being matched by any other pattern.

7.4.2.4 Visualizing Patterns

If you want to see a pattern for a given ligand or group of ligands, you can select the check box in the Mark column for the pattern. Any occurrences of the pattern are marked in the Workspace. You can display markers for more than one pattern, but the markers do not distinguish between patterns. If you want to see the atoms and bonds as well as the markers, select Apply marker offset.

7.5 The Similarity Tab

You can use the options in the Similarity tab to set up and incorporate atom pair similarity scoring in your docking job. Similarity algorithms provide a mechanism for quantifying how alike or unlike two molecules are. This similarity can be a criterion for selecting likely candidates—molecules similar to known actives—from a large molecular database.

Glide uses an atom-pair similarity scoring algorithm. In atom-pair similarity, the two molecules being compared are first processed to generate sets of atom pairs. Each non-hydrogen atom is represented by a similarity type based on the connectivity, bond orders, and formal charges of the molecule. For each pair of similarity types, the shortest path (the path with the smallest number of connections) is determined. The unique combination of

type(atom A) + connectivity distance + type(atom B)

defines one atom pair. All atom pairs for a given molecule constitute the atom pair list for that molecule. The similarity between two molecules is a function of the number of atom pairs that appear in both lists. The similarity function is normalized so that the result is a number between 0.0 (no atom pairs in common) and 1.0 (identical atom pair lists).

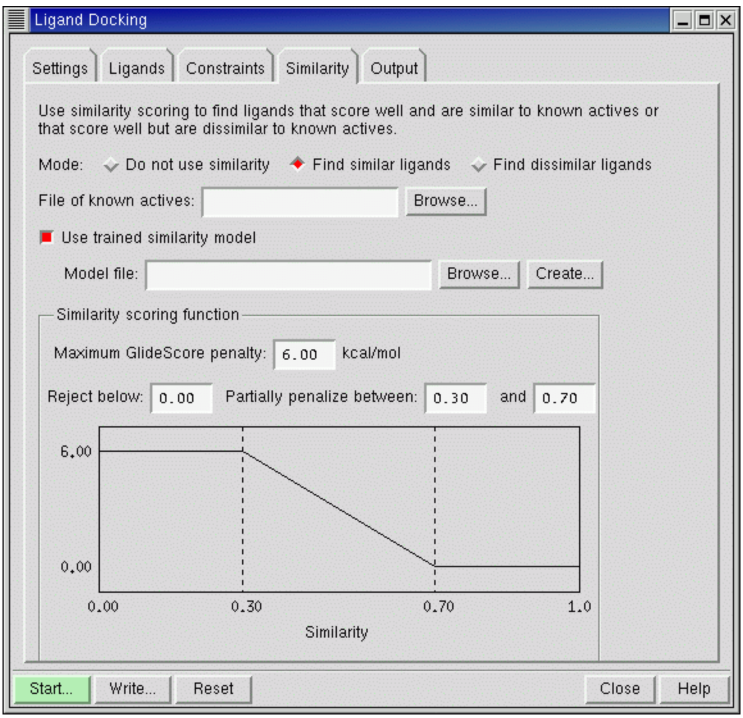


Figure 7.9. The Similarity ***tab of the*** Ligand Docking ***panel.***

Similarity or dissimilarity scoring is combined with the results of Glide docking to produce a composite score. By default, no similarity scoring is performed.

7.5.1 Setting up Similarity Scoring

To set up similarity scoring, you must select a mode and provide a file of known actives. The possible modes are:

- Do not use similarity

  This option is selected by default. The docking job docks and scores ligands without calculating or using similarity scores.

- Find similar ligands

  Select this option to penalize ligands that are different from known actives. In the results of the docking job, ligands that score well and are similar to known actives are ranked high.

- Find dissimilar ligands

  Select this option to penalize ligands that are similar to known actives. In the results of the docking job, ligands that score well and are different from known actives are ranked high.

To specify the file of known active ligands, type the file name in the File of known actives text box, or click the Browse button to open a file selector, in which you can choose the format and navigate to the file. The file must be in Maestro or MDL SD format.

7.5.2 Creating a Trained Similarity Model

In a *trained similarity model*, contributions from atom pair matches to the similarity score are weighted unequally. The weights are determined from a training calculation that uses a set of active ligands and a set of inactive ligands to maximize active-active similarity scores and minimize active-inactive similarity scores. Thus, atom pair matches to inactive ligands are penalized in the similarity score, while atom pair matches to active ligands are rewarded. The weights are stored in a file named *filename*`.wgt`. This file is referred to as the *trained similarity model file*, or just *model file*.

To make use of a trained similarity model, select Use trained similarity model. The controls for specifying the model are activated. If you already have a model file, you can enter the name in the Model file text box, or click Browse and navigate to the file in a file selector.

To generate a trained similarity model, click Create. The Create Similarity Model panel opens, in which you can set up a job to generate a set of optimized weights for a trained model.

To generate the weights file, Glide requires a file of active ligands and a file of presumed inactives. You can specify these files in the File of actives and File of inactives text boxes, or click the Browse button to open a file selector, in which you can choose the format and navigate to the file. The file must be in Maestro or MDL SD format. Information on choosing the files and ligands is given below:

- File of actives

  You can use the same file you specified in the Similarity tab for the file of actives. The file must contain at least two active ligand structures. Best results are obtained with at least 10, but more than 20 are unnecessary and may increase calculation time. To take full advantage of the weighting algorithm, include actives with a wide variety of structures.

- File of inactives

  In addition to known inactives, this file may include untested compounds which are very unlikely to be active. The file of inactives must contain at least one ligand-like structure, but more will improve results. Using 5 to 10 times the number of actives is optimal.

Typical numbers of structures might be 15 structures in the actives file and 150 structures in the inactives file.

If your inactives file is much larger than about 200 structures, or 10 times the number of actives, using all the structures in the inactives file can lead to convergence problems in the training algorithm. To avoid this difficulty you can use a random subset of inactives, by selecting Use random set of inactives and entering an approximate number of inactive ligands in the Approx. number to use text box.

When you have specified the actives and inactives to use, click Start. The Create Similarity Model - Start dialog box opens, in which you can specify a job name, a user name, and a host, then click Start to launch the job. When the job finishes, the weights are written to the trained similarity model file *jobname*`.wgt`, and the file name appears in the Model file text box.

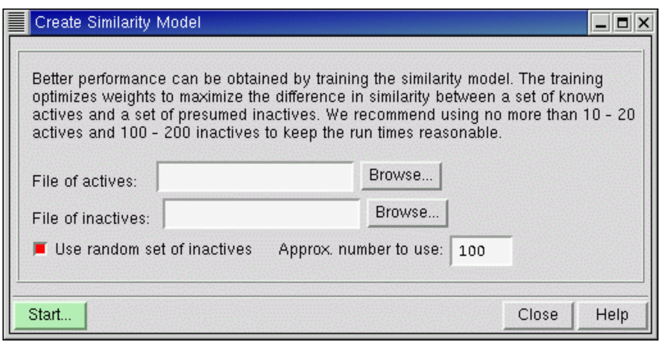


Figure 7.10. The Create Similarity Model ***panel.***

7.5.3 Similarity Scoring Function

Similarity information is incorporated into docking results according to a scoring function that assigns a GlideScore penalty based on a ligand's similarity score, which has been normalized to a value between 0.00 and 1.00. The general shape of the scoring function depends on your choice of similarity mode. If you have selected Find similar ligands, penalties decrease with increasing similarity. If you have selected Find dissimilar ligands, penalties increase with increasing similarity.

The scoring function is controlled by parameters that you can change if necessary. The Similarity scoring function section of the Similarity tab contains the four parameter settings for the similarity scoring function. Beneath these options, the GlideScore penalties are plotted against similarity score, which ranges from 0.0 to 1.0. The plot is updated to reflect a change in the value of a parameter when you press ENTER or click in the next parameter text box.

The scoring function options are described below. In describing features that differ according to similarity mode (Find similar ligands or Find dissimilar ligands), the default is assumed to be Find similar.

Maximum GlideScore penalty *p*

This is the maximum penalty for ligands with low similarity scores (or for ligands with high similarity scores, if Find dissimilar ligands is selected). Changing this number adjusts the relative importance of the similarity score and the basic GlideScore to the combined result. Increasing the maximum penalty increases the importance of similarity relative to docking; decreasing the maximum penalty has the reverse effect. The default value of p, 6.00 kcal/mol, gives similarity score and GlideScore roughly equal weighting, which is generally optimal.

Reject below *r*

Ligands with similarity scores below the threshold r will not be docked. The default value of r is 0.00. Since similarity scores cannot be negative, the default is to dock all ligands regardless of similarity.

If the mode is Find dissimilar ligands, the option is Reject Above: ligands with similarity higher than r will not be docked. The default is 1.00, a score that cannot be exceeded, and therefore corresponds to docking all ligands.

Partially penalize between *m* and *n*

Ligands with similarity scores lower than m receive the maximum penalty. Those with similarity higher than n receive no penalty. Similarity scores between m and n receive a penalty that decreases linearly from the maximum value at m to zero at n, as shown in the scoring function plot. The default value of m is 0.30. The default value of n is 0.70.

In Find dissimilar ligands mode, the default values of *m* and *n* remain the same, but no penalty is applied to ligands with similarity scores of *m* or lower. Scores between *m* or *n* receive increasing penalties, reaching the maximum penalty at *n* and above.

7.6 The Output Tab

The options in the Output tab control the final output of ligand poses that pass successfully through Glide's various scoring stages. The features of this tab are options in a section called Structure output and an Advanced Settings button. Clicking the button opens the Output - Advanced Settings dialog box.

7.6.1 Structure Output Options

In flexible docking runs, Glide appends docked poses to a file named *jobname*`_raw.mae`. The "raw" in the filename indicates that these poses are not sorted by GlideScore. Once the Glide job has docked all the ligands, it runs the `glide_sort` utility script to sort the raw poses and write them to a `_pv.mae` or `_lib.mae` file.

Rigid docking runs sort the poses internally, then, at the end of the job, the sorted poses are written to either a `_pv.mae` or a `_lib.mae` file. The `glide_sort` utility is not automatically used in rigid docking jobs.

The `glide_sort` utility can sort any pose file, whether `_raw.mae`, `_pv.mae`, or `_lib.mae`, using default or alternate criteria. For more information on how to customize the `glide_sort` sorting function, see Section 8.6.1 on page 119.

The options in the Structure output section are described below.

Format

The final list of poses that pass Glide's criteria are written to a multi-structure Maestro-format (`.mae`) pose file. You can select one of two options:

- Write pose viewer file (includes receptor; filename will be <jobname>_pv.mae)

  This version of the pose file, which includes the receptor, is intended for use with the Glide Pose Viewer tool in Maestro.

- Write ligand pose file (excludes receptor; filename will be <jobname>_lib.mae)

  This option includes only the ligand structures in the output pose file. This version of the pose file cannot be used by the Glide Pose Viewer, but may be appropriate if the output poses are intended for input to a subsequent Glide job, or for some other purpose.

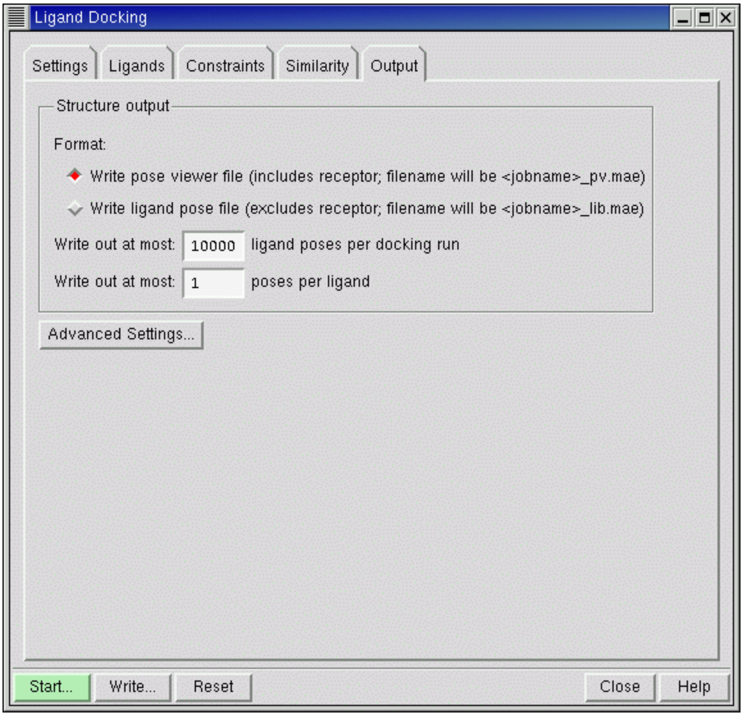


Figure 7.11. The* Output *tab of the* Glide *panel.

A report file that lists critical information about the scoring of the retained poses is also written, to *jobname*`.rept`. Like the pose viewer file or ligand pose file, the report file lists the poses in rank order by the selected final-scoring function.

Write out at most *n* ligand poses per docking run

This text box limits the total number of the predicted best-binding poses written to the sorted pose file. 10 000 poses is the default option.

Write out at most *m* poses per ligand

This text box limits the number of poses per ligand written to the sorted pose file. The default choice of 1 pose per ligand is intended for database screening applications. A larger choice may be appropriate for lead-optimization studies or whenever several "reasonable" poses are wanted; for example, to generate a variety of docked poses for study with Liaison or another post-docking program.

7.6.2 Advanced Settings

In the Output - Advanced Settings box, you can set options to screen out poses that either have too high an energy or are too similar to other poses. The thresholds for rejection of poses are set into two sections, Filter and Clustering.

The Filter section contains a single option, Reject poses with Coulomb-vdW energy greater than x kcal/mol. If the pose has a coulomb-vdW score greater (more positive) than this value, the pose is rejected. The default value is 0.0 kcal/mol. This means that poses that interact favorably with the protein site, however weakly, are retained, whereas poses that interact unfavorably are rejected. Change x to a negative value to reject poses with weakly favorable interactions, or to a positive value to keep poses with mildly unfavorable interactions.

The clustering options determine which ligand poses are sufficiently alike to be considered duplicates. Ligand poses are compared to those previously selected for inclusion in the reported output, and are discarded as duplicates if both of the following criteria are met. This ensures that reported poses are conformationally distinct. The criteria are:

- RMS deviation is less than d Å

  For a pose to be considered a duplicate of one already scored the heavy-atom (nonhydrogen) RMS deviation must be less than r Å. The default RMS deviation threshold for r is 0.5 Å; choose any value greater than 0.0 Å.

- Maximum atomic displacement is less than d Å

  For a pose to be considered a duplicate the maximum atomic displacement must be less than d Å. The default is 1.3 Å; choose any value greater than 0.0 Å.

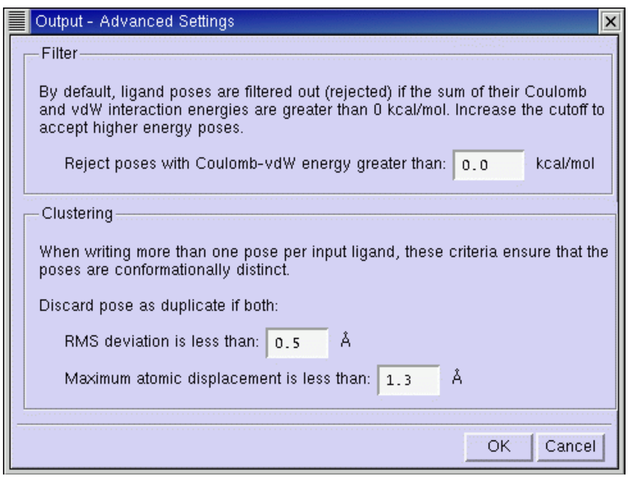


Figure 7.12. The Output - Advanced Settings ***dialog box.***

7.7 The Pose Viewer

The Pose Viewer is not part of the Glide menu, but has its own panel which you open from the Tools menu. You can use the Glide Pose Viewer panel to display the contents of a Pose Viewer file written by Glide and to write out selected poses to another file.

To open the Pose Viewer, choose Glide Pose Viewer from the Tools menu.

The Glide Pose Viewer panel has three tabs. Using the default Poses tab, poses can be displayed with or without the receptor structure, singly or in groups. The list of poses can be stepped through, forward (Next) or backward (Previous). Two standard sets of markers can be displayed by clicking buttons: all hydrogen bonds between the receptor and any non-receptor molecules, and all "bad" or "ugly" contacts between the receptor and non-receptor molecules. To modify the H-bond or contact criteria, or the sets of atoms between which H-bonds or contacts are shown, use the H-Bonds tab or the Contacts tab.

Poses can be modified while in the Workspace (for example, atoms can be deleted), but these modifications apply only to the Workspace display and do not affect the original pose in the pose viewer file. If you modify a pose in the Workspace, select a different pose instead, and then reselect the first pose, it will appear in its original state, without any modifications.

See Chapter 6 of the *Glide Quick Start Guide* for a tutorial exercise in examining Glide data by visualizing bad contacts and hydrogen bonds in the Pose Viewer.

7.7.1 The Poses Tab

This tab includes the following features:

- Open button and File text area

  Click Open to open a file selector and choose a pose file, generally ending in `_pv.mae`, to display. The name of the file appears in the File text area, which cannot be edited.

- Receptor Display option

  The first structure in the selected pose file is assumed to be the receptor. By default, it is displayed. Deselect this option to undisplay the receptor.

  Note: Deselecting or reselecting this option can affect the numbering of the molecules in the Workspace, which can affect the use of molecule numbers in atom set selections and other ASL expressions.

Table 7.3. Description of columns in the Poses table.

Column	Description
Index	The ligand's position in the file. (Note that the first ligand is the second structure in the file since the first structure is the receptor.)
Title	A descriptive name for the ligand, and is imported from the title record of Maestro and SDF files; for PDB files, the filename is used as its title.
Lig # Conf # Pose #	The ligand number, conformation number, and pose number are given for identification.
G-Score E-Model Energy	GlideScore, Emodel, and energy values calculated by Glide for the combination of the posed ligand and the receptor.
HBnd	The number of hydrogen bonds between the posed ligand and the receptor, using the current H-bond measurement criteria. You can change these criteria in the H-Bonds tab.
Good vdW Bad vdW Ugly vdW	The number of van der Waals contacts between the posed ligand and the receptor that meet the current distance criteria for Good, Bad, and Ugly contacts. You can change these criteria in the Contacts tab.

- Pose list

  This table lists all of the conformations and poses of ligands in the file. The row for each pose includes its index number, its title, and various properties of the combination of the posed ligand and the receptor. The column headings are described in Table 7.3.

- Previous button

  This button selects and displays the pose in the row directly above the currently selected row. If multiple rows are selected, the button selects the row above the highest selected row. Clicking Previous in the first row of the list will take you to the last row.

- Next button

  This button selects and displays the pose in the row directly below the selected row. If multiple rows are selected, the button selects the row below the lowest selected row. Clicking Next at the last row of the list will return you to the first row.

- Visualize H-Bonds to Receptor button

  If both the receptor and at least one other molecule (e.g., a ligand pose) are displayed in the Workspace, you can click this button to display markers for hydrogen bonds between the receptor and any other displayed molecules. Clicking the button is equivalent to using the Atom set picking controls in the H-Bonds tab to define Atom set 1 as the receptor and

Atom set 2 as any other molecules in the Workspace. You can change H-bond criteria or other settings in the H-Bonds tab.

- Visualize Contacts to Receptor button

  Click this button to display markers for bad and ugly contacts between the receptor and any other displayed molecules. Clicking the button is equivalent to using the Atom set picking controls in the Contacts tab to define Atom set 1 as the receptor and Atom set 2 as any other molecules in the Workspace. You can change display options, contact criteria, or other settings in the Contacts tab.

- Write Displayed Poses button

  Click to open the PoseWrite panel. At least one ligand pose, or the receptor, must be displayed. The PoseWrite panel is used to write out displayed pose structures to another file.

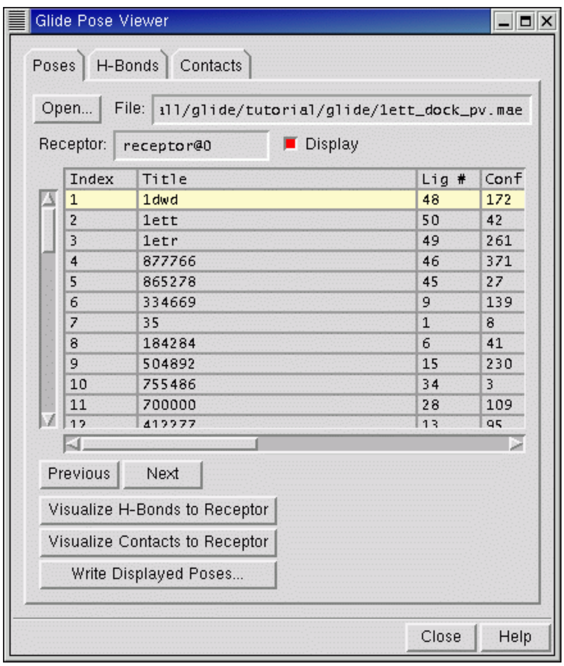


Figure 7.13. The Poses ***tab of the*** Glide Pose Viewer ***panel.***

7.7.2 The H-Bonds Tab

In this tab you can choose to display hydrogen bonds, set the criteria for definition of a hydrogen bond, and select the atom sets between which the hydrogen bonds will be displayed.. The features are:

- Display H-bonds option

  Select this option to display H-bonds in the Workspace; deselect it to undisplay H-bonds. You do not need to display the H-bonds in the Workspace in order to write them to a file.

- Maximum distance text box

  Hydrogen bonds are defined by relations between four atoms: the donor hydrogen atom (H), the acceptor atom (A), the donor atom (D) bonded to H, and another neighbor atom (B) bonded to A. Use this text box to set the maximum distance between atoms H and A that you want to permit in a valid hydrogen bond. The default is 2.50 Å.

- Minimum donor angle text box

  Use this text box to set the minimum donor angle (D-H...A angle) that you want to permit in a hydrogen bond. The default is 120.0°, which is the Maestro default. The value used by Glide is 90.0°.

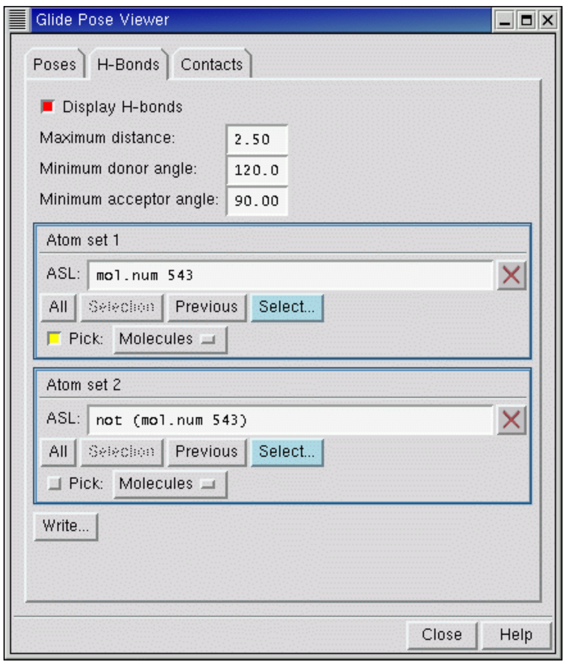


Figure 7.14. The* H-Bonds *tab of the* Glide Pose Viewer *panel.

- Minimum acceptor angle text box

  Use this text box to set the minimum acceptor angle (H...A-B angle) that you want to permit in a hydrogen bond. The default is 90.0°, which is the Maestro default. The value used by Glide is 60.0°.

- Atom set 1 and Atom set 2 picking controls

  Hydrogen bonds can be displayed within a set of atoms (intra-set), or between two sets of atoms (inter-set). To display intra-set H-bonds, use only the picking controls for Atom set 1. If you pick in the Workspace, H-bonds are displayed as you pick. If you click Select to define the atom set using the Atom Selection dialog box, H-bonds are displayed when you click OK. You can also click Selection to include the Workspace selection in the ASL expression, or click Previous to recall the last expression used.

  To display inter-set H-bonds, define atoms for Atom set 1, then for Atom set 2. When you define atom set 2, the intra-set H-bonds in atom set 1 are deleted and replaced by inter-set H-bonds.

- Write button

  Click Write to open the Write H-Bonds panel, in which you can write all H-bonds to a plain text file. The file contains one H-bond per line. Each line contains the atom numbers, H-bond geometry, and related information; separated by a comma, a tab character, or a user-defined delimiter.

Note that the default values are looser than those used by Maestro in the Measurements panel for display of hydrogen bonds. If you want to view hydrogen bonds as defined by Glide in docking, you should change the values in the Minimum donor angle text box and the Minimum acceptor angle text box to 90.0° and 60.0°.

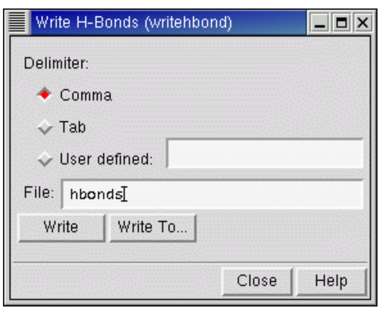


Figure 7.15. The Write H-Bonds ***panel.***

7.7.3 The Contacts Tab

In this tab you can set up the display of contacts between the ligand and the receptor, using the following features:

- Display contacts option

  Select this option to display contacts in the Workspace; deselect it to undisplay contacts. You do not need to display the contacts in the Workspace in order to write them to a file.

- Mark contacts options

  There are three type of contact: good, bad, and ugly. When contacts are displayed, good contacts are marked in green, bad ones in orange, and ugly ones in red. Marking of each kind of contact is controlled by a separate option:

  - Good contacts
  - Bad contacts
  - Ugly contacts

  Since there may be hundreds or thousand of good contacts, by default they are not displayed, while bad contacts and ugly contacts are.

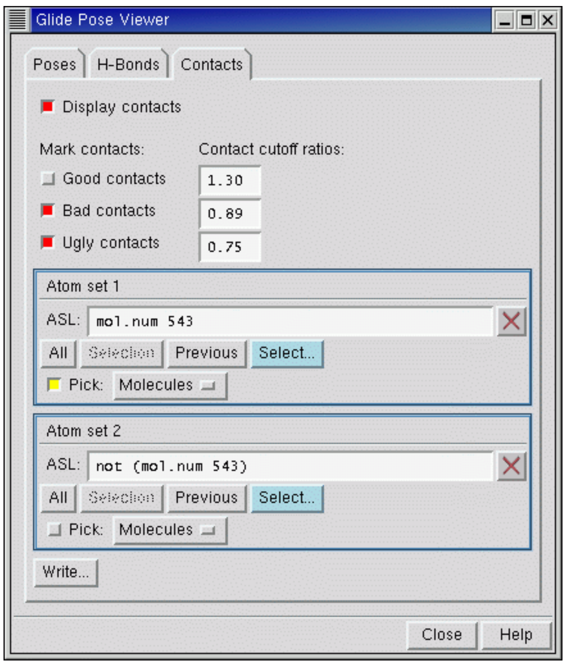


Figure 7.16. The Contacts ***tab of the*** Glide Pose Viewer ***panel.***

- Contact cutoff ratios text boxes

  The criteria for good, bad, and ugly contacts are based on the following formula:

  $$C = \frac{d_{12}}{r_1 + r_2}$$

  where d_{12} is the distance between atomic centers 1 and 2, and r_1 and r_2 are the van der Waals radii of the atoms. C must be monotonically increasing for each of the contact types, that is C(ugly) < C(bad) < C(good). Default values are:

good	1.3
bad	0.89
ugly	0.75

- Atom set 1 and Atom set 2 picking controls

  Contacts can be displayed between molecules within a set, or between two sets of molecules. To display intra-set contacts, use only the picking controls for Atom set 1. If you pick in the Workspace, contacts are displayed as you pick. If you click Select to define the atom set using the Atom Selection dialog box, the contacts are displayed when you click OK. You can also click Selection to include the Workspace selection in the ASL expression, or click Previous to recall the last expression used.

  To display inter-set contacts, define atoms for Atom set 1, then for Atom set 2. When you define atom set 2, the intra-set contacts in atom set 1 are deleted and replaced by inter-set contacts.

- Write button

  Click Write to open the Write Contacts panel, in which you can write all contacts to a plain text file. The file contains one contact per line. Each line contains the atom numbers, contact distance, and related information, separated by a comma, a tab character, or a user-defined delimiter. This panel has the same layout as the Write H-Bonds panel, shown in Figure 7.15 on page 106.

7.7.4 The PoseWrite Panel

The PoseWrite panel allows you to write out to a Maestro format file the pose file structures selected for display in the Glide Pose Viewer panel.

To open the PoseWrite panel, click Write Displayed Poses in the Poses tab.

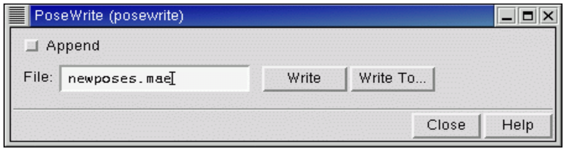


Figure 7.17. The* PoseWrite *panel.

To save a file in the current directory, enter the name in the File text box and press the ENTER key or click the Write button. The file name you enter must end in `.mae`. Maestro will accept absolute (e.g.`/home/joe/file1.mae`) or relative (e.g. `file1.mae`) file names. If you want to save the file to a different directory, click Write To to open a file selector.

The PoseWrite panel offers the following features:

Append

Choose this option to append the poses currently selected in the Pose Viewer panel to the file named in the text box. By default, this option is not selected, and when the file is written it will overwrite any existing file of the same name.

File

Enter the name of the file to write poses to.

Write

Click to write the file to the current directory.

Write To

Click to open a file selector and navigate to the directory in which you want the file to be written.

Running Glide from the Command Line

This chapter contains information on running Glide from the command line.

Although you will usually set up Glide jobs using the controls and settings in the Maestro GUI, you sometimes might want to submit jobs from the command line for the following reasons:

- The command-line scripts can run all full-featured jobs written using the Glide panels in Maestro, and also allow you to override specific run-time values that are not accessible through the Maestro interface.
- Command-line scripts allow you to run Glide jobs when you want.
- Input files and scripts can be modified and jobs can be re-run without reconfiguring and reloading job settings in Maestro. The quickest way to create the input files needed to run a job from the command line is to set up the job in its Maestro panel, click the panel's Write button, and modify the files that are generated. See Section 8.2.2 on page 113 for more information.

8.1 Types of Command-Line Programs

8.1.1 Applications and Utilities

Schrödinger provides command-line applications and utilities to aid in general structure preparation, file format conversion, and database handling. Command-line *applications* are located in the main Schrödinger directory `$SCHRODINGER`. Command-line *utilities* are located in the directory `$SCHRODINGER/utilities`. You may want to add this directory to your path so that they are easy to run by name from the command line.

For usage summary information, use the `-h` (help) option:

```
$SCHRODINGER/command -h
$SCHRODINGER/utilities/utilityname -h
```

For more information about the general-purpose command-line scripts, see Appendix D of the *Maestro User Manual*.

8.1.2 Impact and Other Glide Commands

For Glide, as for other Schrödinger applications that use the Impact computational engine, the `impact` command can run most types of jobs. Both receptor grid generation and ligand docking jobs are run using the `impact` command.

Glide also has a set of its own command-line applications and utilities. Protein preparation jobs use the command-line application `protprep`, which calls the utilities `pprep` and `impref`. While ligand docking jobs can be started using `impact`, if you have a large set of ligands to dock and so want to distribute docking calculations over multiple CPUs, you should use the `para_glide` command-line application. The `$SCHRODINGER/utilities` directory contains two additional Glide utilities, `glide_sort` and `glide_rescore`, which are also summarized in this chapter.

8.2 General Command-Line Job Information

8.2.1 Job Files and Directories

Location of Files and Working Directory

For Glide jobs, Maestro normally writes input files to the directory from which you launched Maestro (the *Maestro working directory*). Impact also normally writes its output files to the same location, though Impact input files and the Glide interface allow you to specify an arbitrary location for grid files.

Force Fields

The molecular mechanics force field used in Glide 4.0 is the OPLS_2001 version of OPLS-AA. OPLS_2001 is designed to work with automatic atom-typing, and is incompatible with template mode.

File Name Conventions

A typical Impact job has one command-script file (*jobname*`.inp`), one or more structure files (*jobname*`.mae`, *jobname*`.pdb`, or *jobname*`.sdf`), and after execution, several output files (e.g., *jobname*`_out.mae` for structure files and *jobname*`.out` for textual data).

If a file already has the name of an output file, in many cases Impact renames the old file with a numerical extension (*filename*`.out.01`, *filename*`.out.02`, and so on) for archival purposes. The new job's output is then written to the base name (*filename*`.out`). If you do not need the old files, you can remove them.

Some files, such as *jobname*.log files, are newly written each time Impact runs a calculation. Likewise, old *jobname*_pv.mae files are overwritten.

In addition, *jobname*_out.mae files are *not* produced by default for Glide jobs—Glide writes intermediate Maestro-format structure output to *jobname*_raw.mae files, which are incremented.

Table 8.1 contains descriptions of the various files generated during a Glide docking run. For more information, see the Maestro online help or the *Impact Command Reference Manual*.

Table 8.1. Input and output files for Glide docking jobs.

File	Description
jobname.inp	Impact input file or script. Impact input files are formatted plain-text files written in the Impact input file language, DICE. Maestro creates Impact input files before job submission. You can create or edit them manually with a text editor.
jobname.mae	Maestro format file containing input structures for docking.
jobname.log	Impact log file. If specified, a .log file captures standard output and standard error messages in text form. This file is overwritten during subsequent runs.
jobname.out	Impact output file, containing output from standard output but not standard error. Output files are appended with numerical extensions when the input file is used again. Up to 99 output files are retained.
jobname.rept	Plain text file containing a table of ranked poses, scores, and score components.
*jobname*_lib.mae	Glide structure output file produced in HTVS mode, in Maestro format.
*jobname*_pv.mae	Glide pose-viewer file, in Maestro format. Contains the receptor structure and followed by all output ligand poses ranked by their score.
*jobname*_raw.mae	Glide's intermediate structure files, containing unranked ligand poses.

8.2.2 Running Jobs From the Command Line

The SCHRODINGER environment variable must be set to run jobs. You can define SCHRODINGER as follows:

csh/tcsh: setenv SCHRODINGER *installation-directory*

bash/ksh: export SCHRODINGER=*installation-directory*

Entering ls $SCHRODINGER at the command prompt will list the Schrödinger installation directory contents, including the Maestro startup script (maestro) and the Impact startup script (impact).

Unless otherwise specified, Schrödinger applications and utilities run under Schrödinger's Job Control facility and are automatically run in the background. You need not add an `&` at the end of the commands to have them run and immediately return your command prompt. The `-WAIT` option of the `impact` command forces the shell to wait until the job is finished, so you can embed such commands in other scripts.

8.2.3 Using Job Control Commands

Once your jobs are launched, you can monitor their progress using the Monitor panel in Maestro. The command `$SCHRODINGER/jobcontrol` can also be used. It has many options, but the two most useful options are:

```
$SCHRODINGER/jobcontrol -list
```

which will show the status of all your jobs, and:

```
$SCHRODINGER/jobcontrol -kill
```

to terminate any job and its subjobs, if any exist.

For a summary of `jobcontrol` options, use:

```
$SCHRODINGER/jobcontrol -h
```

For more information, see the *Job Control Guide*. For an introduction to running and monitoring jobs in Maestro, see Section 2.10 on page 28.

8.3 Protein Preparation: protprep

If you do not yet have receptor and ligand structure files for the structures in the Workspace, to write the structure files.

Protein preparation jobs can be run from the command line using the `protprep` application and input files with the receptor and co-crystallized ligand structures. A usage summary for protprep appears in this section. To generate the structure files, include the receptor and ligand in the Workspace, then click the Write button in the Protein Preparation panel.

Usage summaries for the `pprep` and `impref` utilities, which are called by protprep and need seldom be used directly, are in Section 8.8.

The `$SCHRODINGER/protprep` application has command-line options corresponding to features of the Maestro Protein Preparation panel. By setting the `-mode` option, you can use protprep to run preparation-only or refinement-only jobs as well as combined preparation-refinement jobs (the default). The command `protprep -h` displays the usage summary that appears in this section.

Syntax:

`$SCHRODINGER/protprep [`*options*`]` *input-file*

input-file is the file containing the protein to be prepared or refined. This file must be in Maestro format. When doing a refinement only job (`-mode refine`) this file can contain a protein-ligand complex.

Options:

General Options:

`-j` *jobname*	Override the default job name derived from *input-file*. This allows you to choose an output job name that is different from the *input-file* name.
`-l` *ligand-file*	Specify a file containing a ligand in the protein's active site. This file must be in Maestro format.
`-m` *mode* `-mode` *mode*	Select mode, where *mode* is one of the following: `prep` Preparation only. `refine` Refinement only. `both` Preparation and refinement (default).
`-debug`	Print verbose (debugging) output.
`-HOST` *host*	Run the job on a remote host.
`-LOCAL`	Run the job in the current directory, rather than in a temporary scratch directory.
`-WAIT`	Wait until the job finishes before returning the command prompt.
`-NICE`	Run the job at reduced priority.
`-HELP | -h`	Print usage message and exit.

Preparation Stage Options:

`-min-recep-only`	Minimize total charge of receptor only.
`-skip-sidechain-corr`	Skip correction of conflicting side-chain forms.
`-cavity-8-12`	Set cavity distance range to 8-12 Å.
`-salt-bridge-dist`	Leave residue pairs forming salt bridges within *dist* Å ionized; default is 3.5 Å.
`-ionization-range`	Leave residues within *dist* Å of ligand ionized.
`-hbond-dist`	Set H-bonding distance; default is 3.45 Å.

Refinement Stage Options:

`-r` *rmsd*	Maximum RMSD allowed for refinement; default 0.3.
`-keep`	Keep intermediate structure files.
`-separate`	Write out refined protein and ligand structures separately, rather than in one combined structure.

8.4 Receptor Grid Generation: impact

Using Maestro is the best way to write Glide job scripts, even if you intend to run them from the command line. The scripts are very intricate and are subject to change with each new distribution of the program. To run a Glide job script, enter:

`$SCHRODINGER/impact -i` *jobname*`.inp [-o` *logfile*`]`

By default, the log information is written to *jobname*`.log`, but if you want to use a different file name, use the `-o` option.

If your protein has more than 8000 atoms and you are making grid files (but not if you are just docking ligands), you will also need to include the `-s huge` option in the command.

8.5 Ligand Docking: impact and para_glide

The `para_glide` application can be used to launch a large Glide docking job, distributing the ligand database over a number of processors. See Section 8.5.2 for more information.

8.5.1 The impact Command: Usage Summary

The `impact` options that you can specify when initiating Glide receptor grid generation and ligand docking jobs from the command line are described in Table 8.2 and Table 8.3. This list also includes `impact` keywords with more general applications. To view the usage summary information, define the `SCHRODINGER` environment variable and enter `$SCHRODINGER/impact -h` in a terminal window.

Syntax:

`impact [`*options*`] [[-i]` *input-file*`]`

Table 8.2. `Impact` *command options*

Option	Description
`-h`	Print usage summary and exit
`-v`	Print version number of startup script and exit
`-i` *input-file*	Impact input file, conventionally ending in `.inp`. If the *input-file* argument does not end in `.inp`, Impact looks first for *input-file* as specified. If that file doesn't exist, it then looks for *input-file*`.inp`. If `-i` is omitted, then *input-file* **must** end in `.inp` and must be the last argument in the command line.
`-o` *output-file*	File for writing output and log messages. If this option is omitted, Impact names the log file *jobname*`.log`, where *jobname* is taken from the Impact input file name.
`-s` *size*	Use specific "size" version of the Impact executable. Acceptable values for *size* are `medium` or `huge`. If omitted, `medium` is assumed in most cases; it is valid for up to 8000 atoms or 8000 bonds. The `huge` option accommodates up to 40000 atoms or 40000 bonds.

Table 8.3. Schrödinger Job Control options

Option	Description
`-HOST` *host* `-HOST` *host:n* `-HOST "`*host1 host2*`"`	Specify one or more remote hosts with the number of processors (*n*) to use. Can also be used to specify a batch queue to submit the job to, or a collection of hosts for distributed or parallel jobs. Default is to run on the local host. See Section 8.2.2.
`-NO_REDIRECT`	Do not run `impact` under Job Control. If you use this option, you must ensure that your input and output files are in the appropriate location, because none of the functions of Job Control are performed.
`-USER` *user*	Specify the user name for the selected hosts. Default is to use the local user name.
`-WAIT`	Do not return control to the shell until the job finishes. This is useful in command scripts in which you have specified actions to take only after the Impact job finishes.
`-WHICH`	This switch is a diagnostic tool printing the available Impact installations you can use for the local machine. The job itself is not submitted. The first one listed is the default path; the options `-REL`, `-VER`, and `-ARCH` can direct your job to use a different installation.
`-REL` *release*	This option selects a specific version number of Impact to use. The default is the latest (highest number). Formats like `-REL v4.0`, `-REL 35000`, and `-REL 27` are supported.

Table 8.3. Schrödinger Job Control options (Continued)

Option	Description
`-VER` *pattern*	If you have multiple installations installed, you can specify a pattern with the `-VER` option that matches the installation path to use for your job. The default installation is the one printed by `-WHICH`.
`-ARCH` *platform*	If you have more than one architecture installed for a given system, e.g., AIX-com and AIX-pwr3, then this flag can be used to select either of them, such as `-ARCH pwr3`.
`-LOCAL`	Force remote jobs to run in a local directory, rather than on the remote host. Only active when `-HOST` is used.

8.5.2 para_glide

Submits batches of ligand structures to multiple processors for Glide docking jobs.

Syntax:

`$SCHRODINGER/para_glide -i` *input-file* `[`*options*`]`

Table 8.4. Options for para_glide.

Option	Description
`-n` *njobs*	Number of subjobs to prepare.
`-f` *firstlig*	First ligand to include.
`-l` *lastlig*	Last ligand to include.
`-j` *jobnum*	Subjob number to prepare.
`-x`	Launch jobs after writing input files.
`-s`	Split input ligand file by subjob.
`-o`	Have log file written directly to output directory (only meaningful if `-x` option is also used).
`-h`	Print help message and quit.
`-v`	Print version number and quit.

The `para_glide` utility splits the Glide job specified in the *inp-file* into smaller subjobs for distributed execution. The ligands between *firstlig* and *lastlig* (inclusive) are separated into *njobs* equal-sized batches. If omitted, *njobs* defaults to 1, *firstlig* defaults to 1 and *lastlig* defaults to 0, which is interpreted to mean the final ligand in the ligands file.

Each use of `para_glide` creates two scripts: *jobname*`_report.sh` and *jobname*`_status.sh`. The *jobname*`_report.sh` script collects the output (poses) from subjobs created by `para_glide`, and produces a single pose file and a single report file that summarizes the best poses in the entire job suite. The subjob results are stored in subdirectories of the working directory, named *jobname_firstlig_lastlig*, where *firstlig* and *lastlig* are the indexes of the first and last ligands in the subjob. The *jobname*`_status` script can be run while the job suite is running or afterward. It summarizes the disposition of each job: whether it finished normally, died, was terminated, stopped, and so on, using the conventional Schrödinger job control terms. (See Chapter 5 of the *Job Control Guide* for information about job monitoring and job control.)

The `-j` option is useful for preparing only a single subjob. A value of 0 is equivalent to not specifying `-j` at all, and all subjobs will be printed. Negative values are not permitted.

By default, all jobs use the same input ligand file, each job reading out of it just the ligands pertinent to that job. If the `-s` option is given, a new ligand file is written for each subjob, containing only the ligands for that subjob. This is likely to be more efficient if there are a large number of ligands.

If the `-x` option is given, then the jobs are launched after the input files are written. Any additional arguments you give on the command line are passed on to the `impact` command. Therefore, you can have the jobs run on a remote machine by specifying `-HOST` *hostname*.

8.6 Glide Utilities

8.6.1 glide_sort

Re-ranks Glide poses by custom criteria or combines job outputs into one file.

Syntax:

`$SCHRODINGER/utilities/glide_sort` *mode* `[`*options*`]` *Glide-pose-files*

Modes of Operation:

At least one of these modes is required:

`-o` *output-file*	Write the best-scoring poses to *output-file.*
`-r` *report-file*	Create a report of the best scores in *report-file.*
`-R`	Write a report of the best scores to standard output.

Options:

Sorting

-use_dscore	Default. Sort poses based on the "docking score" in Glide output poses."Docking score" is a placeholder for the property on which you would like to sort poses. Initially it is equal to GlideScore, but glide_rescore can be used to replace it with other values (see Section 8.6.2.)
-use_gscore	Sort poses based on GlideScore. Overrides -use_dscore.
-use_cvdw	Sort poses based on Coulomb-van der Waals energy, E(CvdW). Overrides -use_dscore.
-use_emodel	Sort poses based on model energy score, Emodel. Overrides -use_dscore.
-use_prop *prop*	Sort poses based on the specified user-defined numerical property, from lowest to highest values. Overrides -use_dscore.
-nosort	Don't sort the poses.

Output

The "best" pose is defined by the property used for sorting.

-n *nreport*	Retain only the *nreport* lowest-scoring poses.
-norecep	Don't include the receptor structure in output files.
-best	Keep only the single best pose for each ligand in each input pose file.
-best-by-lignum	Keep only the single best pose for each ligand with a given *lignum* value.
-best-by-title	Keep only the single best pose for each ligand with a given title.
-best-by-prop *prop*	Keep only the single best pose for each ligand with a given value of the specified property *prop*.
-h	Print help message and exit.
-v	Print version number and exit.

Custom Scoring Function

Setting any of these custom scoring function terms causes glide_sort to sort only on this custom function instead of the standard -use_ sorting options.

-gscore *coef*	GlideScore coefficient (default = 0.0) for custom scoring function.
-cvdw *coef*	E(CvdW) coefficient (default = 0.0) for custom scoring function.
-internal *coef*	E(internal) coefficient (default = 0.0) for custom scoring function.
-emodel *coef*	Emodel coefficient (default = 0.0) for custom scoring function.
-offset *coef*	Energy offset (default = 0.0) for custom scoring function.

Filter

-hbond_cut *cutoff*	Filter cutoff for H-bond energy (default = 0.0).

`-cvdw_cut` *cutoff*	Filter cutoff for E(Cvdw) (default = 0.0).
`-metal_cut` *cutoff*	Filter cutoff for metal-ligation energy (default = 0.0).
`-emodel_cut` *cutoff*	Filter cutoff for Emodel (not used by default).
`-nofilter`	Don't use filter cutoffs at all.

8.6.2 glide_rescore

Replaces the "docking score" properties in Glide pose output files with different values, so that the `glide_sort` "best-by-title" option can be used to combine different screens. See Section 8.6.1.

Syntax:

`$SCHRODINGER/utilities/glide_rescore [`*options*`]` *pv-or-lib-files*

Options:

`-rank`	Replace "docking_score" with ligand rank (default mode).
`-offset` *value*	Replace "docking_score" with GlideScore plus this offset.
`-average`	Calculate the average GlideScore over all the poses; no output besides this average is produced.
`-top` *number*	Average only the top *number* poses.
`-every` *number*	Print running averages every multiple of *number* poses.
`-o` *output-file*	Output to this file name, instead of default name (*input-file*`.rank.mae` or *input-file*`.offset.mae`).
`-h`	Print help message and quit.
`-v`	Print version number and quit.

Only one of `-rank`, `-offset`, and `-average` can be used at a time. If none is specified, `-rank` is assumed.

Using `-top` and/or `-every` implies `-average` mode.

8.7 Examining Results From the Command Line

While Maestro provides the Pose Viewer interface to visualize high-scoring poses, you can also see the numerical results for these poses in the *jobname*`.rept` output file. A score-in-place calculation writes a *jobname*`.scor` report file instead, and no structural output for the Pose Viewer. The results are stored as Maestro properties in the Pose Viewer file (*jobname*`_pv.mae`) or ligand database file (*jobname*`_lib.mae`), and can be displayed in the Maestro Project Table.

8.8 Additional Glide Utilities

The two protein preparation utilities in this section are now called by `protprep`. There should be little need to use `pprep` or `impref` at the command prompt. The `protprep -mode` option allows you to run a preparation-only or refinement-only job without invoking `pprep` or `impref` directly. See Section 8.3.

8.8.1 Usage Summary for pprep

The `pprep` utility is called by `protprep` to run the preparation stage of the protein preparation process. The preparation stage consists largely of adjusting the protonation states of the receptor structure. There should be little need to run `pprep` directly. To run a preparation-only job, use `protprep -mode prep`.

Syntax:

`$SCHRODINGER/utilities/pprep [`*options*`]` *proteinfile*`.mae`

Options:

`-i` *idis*	Leave residue pairs forming salt bridges within *idis* ionized; default is 3.5 Å.
`-l` *ligfile*	Read ligand mae file *ligfile*.
`-n` *outfile*	Specify non-default (*lig*`R.mae`) name for output file with neutralized residues.
`-p`	Print verbose output.
`-r`	Minimize total charge of the receptor only.
`-t`	Skip correction of conflicting side-chain forms.
`-w` *wdis*	Leave residues within *wdis* of ligand ionized.
`-H` *hbonddist*	Set H-bonding distance; default 3.45 Å.
`-L`	Set cavity distance range to 8-12 Å.
`-v`	Print version number and exit.
`-h`	Print usage message and exit.

8.8.2 Usage Summary for impref

The `impref` utility is invoked by `protprep` to run the refinement stage of protein preparation. It uses Impact to perform restrained optimizations of the ligand-receptor complex. There is little need to run `impref` directly. To run a refinement-only job, use `protprep -mode refine`.

Syntax:

```
$SCHRODINGER/utilities/impref [options] input.mae
```

Options:

`-k`	Keep Impact minimization `*.inp`, `*.log`, and `*.mae` files.
`-l` *ligfile*	Read ligand from file *ligfile*, instead of *input*`.mae`. If this option is used, *input*`.mae` must be the protein structure alone. If this option is not used, *input*`.mae` must be the protein/ligand complex.
`-r` *rmsd*	Specify maximum RMSD allowed; default is 0.3.
`-s`	Write out protein and ligand separately. Requires `-l` *ligfile*.
`-op` *file*	Output protein or complex file. Default is *input*`_ref.mae`.
`-ol` *file*	Output ligand file (when `-s` and `-l` used.) Default is *ligfile*`_ref.mae`.
`-v`	Print version number and exit.
`-h`	Print usage message and exit.

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the tab that is displayed in a panel, click the Help button in the panel. The Help panel is opened and a relevant help topic is displayed.
- For other information in the online help, open the Help panel and locate the topic by searching or by category. You can open the Help panel by choosing Help from the Help menu on the main menu bar or by pressing CTRL+H.

  To view a list of all available Glide–related help topics, choose Glide from the Categories menu of the Categories tab. Double-click a topic title to view the topic.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Tutorial*, for a tutorial on the basic features of Maestro
- *Maestro Command Reference Manual*, for information on Maestro commands
- *Glide Quick Start Guide*, for a tutorial guide to using Glide
- *Impact Command Reference Manual*, for Impact command syntax
- Frequently Asked Questions pages, at
  https://www.schrodinger.com/Glide_FAQ.html

The manuals are also available in PDF format from the Schrödinger Support Center. Information on additions and corrections to the manuals is available from this web page.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail:	help@schrodinger.com
USPS:	101 SW Main Street, Suite 1300, Portland, OR 97204
Phone:	(503) 299-1150
Fax:	(503) 299-4532
WWW:	http://www.schrodinger.com
FTP:	ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information, most of which can be obtained by entering `$SCHRODINGER/machid` at a command prompt:

- All relevant user input and machine output
- Glide purchaser (company, research institution, or individual)
- Primary Glide user
- Computer platform type
- Operating system with version number
- Glide version number
- Maestro version number
- mmshare version number

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120 West 45th Street
32nd Floor
New York, NY 10036

101 SW Main Street
Suite 1300
Portland, OR 97204

3655 Nobel Drive
Suite 430
San Diego, CA 92122

Dynamostraße 13
68165 Mannheim
Germany

QuatroHouse, Frimley Road
Camberley GU16 7ER
United Kingdom

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